

SYNTHESIS AND STUDY OF SOME THIAZOLE DERIVATIVES
AS POSSIBLE ANTITUBERCULAR AGENTS

THESIS SUBMITTED TO
UNIVERSITY OF BOMBAY

FOR THE DEGREE OF
MASTER OF PHARMACY
IN
PHARMACEUTICAL CHEMISTRY

SUBMITTED BY
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UNDER THE GUIDANCE OF
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HAFFKINE INSTITUTE FOR TRAINING, RESEARCH & TESTING
BOMBAY

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A
THESIS

Submitted to

The University of Bombay

For

The Degree of

MASTER OF PHARMACY

In

The Faculty of Technology

(PHARMACEUTICAL CHEMISTRY)

By

Sragdhara V. Nalavde

B. Pharm.

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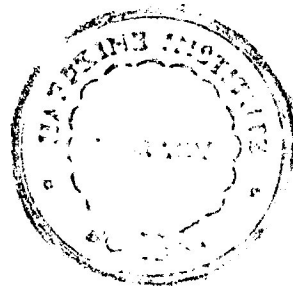
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Department of Chemotherapy

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(1989)



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STATEMENT UNDER UNIVERSITY RULE

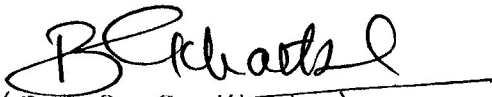
As required by the University Rule No. 0.412 and 0.413, I state that the work presented in this thesis is original in nature and so far to the best of my knowledge has not been submitted for any degree to this or any other University.

Wherever reference has been made to the work of others, it has been clearly indicated along with the source of the information in the "References".

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PART I

INTRODUCTION

INTRODUCTION



Mycobacterial diseases are the most ancient of man. Tuberculosis is a disease as old as mankind itself. It has been described as "King of Diseases" in the Vedas and was mentioned by Charaka and Sushruta, about 600 B.C. Hippocrates and other Greek physicians (400 B.C. - A.D. 100) studied tuberculosis and recommended a change of climate, a form of treatment still used. The mycobacterial diseases are the most protracted of all infections, whether treated or untreated and require the longest therapy (540-730 days or more).

Tuberculosis is prevalent in most of the socio-economically backward parts of the world. Due to this, eradication of the disease, throughout the world has become difficult. The global estimate for tuberculosis cases are very crude. It is estimated that every year about 10 million individuals develop clinical tuberculosis and 3 million die from the disease.¹

The gravity of the disease was felt by various health organizations and individual Governments and this led them to establish several good control programmes and health services for its people. Due to this, there was reduction in the risk factors for tuberculosis. The

reduction rates are given in Table 1.¹

TABLE - 1

Parts of the world	Reduction rates for T.B. cases
Industrialized countries	10 %
Developing countries	5-10 %
Underdeveloped countries*	0-4 %

The last group (*) mentioned above, comprises most of the world's population and has the highest prevalence of tuberculosis, as well as a population growth of 2-3 % per year. Hence, the general reduction of the global tuberculosis problem, in absolute number of cases, is very small.

Tuberculosis is a major public health problem in India. Survey conducted by NICD, Delhi indicates that nearly 1.5% of the total population is affected by this disease and about 2.5 million new cases are reported every year. The statistics of the number of reported cases and deaths per year in this decade due to tuberculosis in India are as follows :

	1981	1982	1983	1984	1985	1986	1987
ases	766914	841917	881328	987013	903817	853202	852334
aths	10019	9021	10781	11112	9933	9425	8796

(Data is taken from "Health Information India-1986", Central Bureau of Health Intelligence Directorate General of Health Services, Ministry of Health & Family Welfare, Govt. of India).

Since tuberculosis is non-notifiable disease, many more tuberculosis cases and deaths in remote village areas remain unreported. So actual statistical data is not available. Reported statistics show that tuberculosis is still a scourge among the people of India. Realizing the intensity of this health problem, Government of India had already taken major steps to control this disease, which is discussed on page No. 4.

Statistical data shows tuberculosis is the global health problem. Hence, a need for comprehensive tuberculosis control programme on a country-wide scale through the network of existing health services, was felt by W.H.O. Such programme was formulated in early 1960s in the Eighth Report of the W.H.O. Expert Committee on Tuberculosis, and reaffirmed in the Nineth Report in 1974. Disease control programmes included case-findings, chemotherapy of patients and BCG vaccination. The W.H.O. initiated global immunization effort in 1974 under the banner of the Expanded Programme on Immunization. At present, 60% children of the world are immunized against tuberculosis under this programme. "Health for All, by 2000 A.D." is the declaration of W.H.O. To achieve this, W.H.O. has set target for raising the immunization level of at least 80 % of all the children of the world, by 1990 and at least 90 % by the year 2000. As per W.H.O.'s Eighth

General Programme of work (1990-1995), the target set for developing countries is that by 1992, 80% of the developing countries will have incorporated case findings and treatment activities in their tuberculosis control programmes and by 1995, the epidemiological effectiveness of this programme would be increased, by earlier case detection and closer supervision.

In India, National Tuberculosis Control Programme was launched to reduce the suffering of patients, number of cases and death rate, with the ultimate aim to make the occurrence of infection negligible, to such an extent that it ceases to be an major public health problem. Under this programme expansion of tuberculosis case findings, treatment, establishment of new tuberculosis beds, new district tuberculosis centres and preventive activities including BCG vaccination for infants was planned.

Thus, the prevention or control of this major health problem is directly related with the implementation of political and technological factors. The powerful weapon to curb this menace is effective public counselling and implementation of vaccination. But the only way of treatment of the cases diagnosed is effective chemotherapy which must be easily and economically

accessible to the needy and the sick.

BIOLOGY OF TUBERCULOSIS BACILLI,

Tuberculosis is an infectious disease, caused by several species of mycobacteria, collectively termed the tubercle bacilli. The most important human pathogens of this class are Mycobacterium tuberculosis (M. tuberculosis) and Mycobacterium bovis. M. tuberculosis is a member of the family Mycobacteriace and order Actinomycetales. The genus mycobacterium includes both saprophytic and pathogenic species. The saprophytic mycobacteria are widely distributed in nature, soil, water, on grass, skin of man and other animals. The pathogenic species may produce disease, in a variety of mammals, birds, reptiles, fish and other cold blooded animals. Many mycobacteria that are potentially pathogenic for man have not been named and are commonly referred to as 'unclassified' or 'atypical'.

M. tuberculosis is thin rod shaped organism with breadth 0.2 to 0.5 μ and length in the range 2 to 6 μ . It may be straight or slightly curved. It is non-motile, non-sporogenous and non-encapsulated. All mycobacteria grow and metabolise slowly and are more resistant to variety of deleterious influences than other bacteria. After standing they resist decolorization with mineral acids, and therefore, are referred to as acid-fast.

Tubercle bacilli produce infections of the lungs, lymph nodes, bone joints, meninges, genito-urinary system, spleen, liver, skin and peritoneum. But human pulmonary tuberculosis is the most common among these infections.

CHEMOTHERAPY OF TUBERCULOSIS :

Attempts to find suitable chemotherapeutic agents for tuberculosis started almost from the time Koch (1882) announced the discovery of the etiological agent of this disease. Until 1940, no effective chemotherapeutic agent was available for treating tuberculosis. The treatment mainly consisted of rest, fresh air and good food. Surgical methods like phrenic nerve avulsion, artificial pneumothorax and pneumoperitoneum were widely employed. The discovery of para-aminosalicylic acid by Bernheim in 1941 was the first step in the development of effective antitubercular agent. The two commonly used agents, streptomycin and isonicotinic acid hydrazide (INH) were discovered in 1944 and 1952. When these drugs were administered singly for long period of time, toxicity problems and development of resistant microorganisms seriously limited their usefulness. This led to the phase treatment for control of the tuberculosis. The initial or intensive phase is the period during which the host's

population of organisms is largest and drugs are administered for minimum period of 4 weeks in case of small lesions and 8-12 weeks in moderate to extensive lesions. The continuation phase is that period, after the population of organisms has been markedly decreased during intensive phase, when the number of acid-fast bacilli is further reduced towards "sterile" state. Continuation phase treatment is given for minimum period of 10 to 12 months and maximum for 18 to 24 months depending on the state of the disease.

The drugs are administered in combination, in phase treatment, in order -

1. to delay the development of bacterial resistance,
2. to prolong the effective therapy, and
3. to achieve maximum benefit with minimum toxicity .

But, if the drug combination is not proper, then failure of the phase treatment is possible. Since at the start of the treatment, bacterial population is greater, greater is the chance of development of secondary drug resistance. Hence, initial treatment is always with multiple drugs and preferably all bactericidal. INH + rifampicin is the most effective antitubercular combination. To enhance the effectiveness of this combination and avoid the consequences of primary and secondary resistance, one

or two supplementary drugs, in initial intensive phase of treatment are added. If only one bactericidal drug is selected in 3 drug regime and when drug resistance develops during treatment, it is invariably against that bactericidal drug and bacterial relapse occurs. Hence, the treatment is initiated with three standard drugs as the bacterial resistance to one of drugs is most likely.

The recommended three drug regimes for initial phase of treatment are -

- 1) INH (200-300 mg) + RIF (450-600 mg) + SPM (0.75-1.0 g)
- 2) INH (200-300 mg) + RIF (450-600 mg) + ETB (15 mg/kg)
- 3) INH (200-300 mg) + SPM (0.75-1.0 g) + PYZ (1.5-2.0 g)
- 4) INH (200-300 mg) + SPM (0.75-1.0 g) + ETB (15 mg/kg)

The recommended daily, two drug regimes for continuation phase treatment are -

- 1) INH (200-300 mg) + RIF (450-600 mg)
- 2) INH (200-300 mg) + ETB (15 mg/kg)
- 3) INH (200-300 mg) + SPM (0.75-1.0 g)
- 4) INH (200-300 mg) + PAS (10.0 g)

contd...

5) INH + THA
 (200-300 mg) (150 mg)

INH = Isoniazide; RIF = Rifampicin; SPM = Streptomycin;
ETB = Ethambutol; PYZ = Pyrazinamide;
PAS = Para-aminosalicylic acid; THA = Thiacetazone.

The chemotherapeutic agents available for treatment of tuberculosis can be divided into two groups such as standard drugs or first line drugs and reserve drugs or second line drugs.

1) Standard drugs are those, which are most effective and hence used in the initial treatment. These are isoniazide, streptomycin, rifampicin, ethambutol, thiacetazone and para-aminosalicylic acid.

2) Reserve drugs are the ones, which are not as effective as standard drugs but are used when standard drugs are ineffective due to toxicity symptoms or resistance problem. These include pyrazinamide, ethionamide, capreomycin, viomycin, kanamycin and cycloserine.

The antitubercular drugs can also be classified as bactericidal and bacteriostatic.

<u>Bactericidal</u>	<u>Bacteriostatic</u>
Isoniazide	Ethambutol
Rifampicin	PAS
Pyrazinamide	Cycloserine
Streptomycin	Capreomycin
Ethionamide	
Kanamycin	

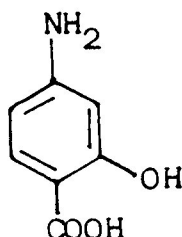
The drugs currently available for treating tuberculosis are quite effective as far as bacterial killing is concerned and in recent years the duration of chemotherapy for this disease has also been reduced considerably. In spite of this, drug resistant strains of the mycobacteria continue to occur, largely as a result of use of routine practice of single drug and unscientific combination of available drugs. Problems of drug compliance and cost also bring out the necessity for regimens of even shorter durations than those currently employed. Thus, the need for continued efforts to establish newer and better drugs is, therefore, evident.

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REVIEW OF LITERATURE

REVIEW OF LITERATURE

1. p-Aminosalicylic acid (PAS) :



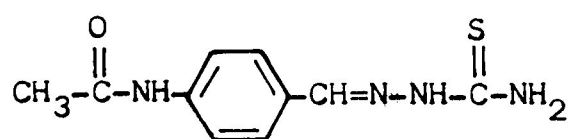
Lehmann² proposed p-amino salicylic acid as a chemotherapeutic agent for tuberculosis in 1946, after it was shown in 1941 that benzoic and salicylic acids increase the oxygen uptake of virulent tubercle bacilli.³ This drug is useful only in tuberculosis and not in other infections.⁴ It stops the growth of actively multiplying tubercle bacilli both in vivo and in vitro. But it is far less potent than isoniazide and streptomycin and a continuous blood level of the compound has to be maintained to achieve a tuberculostatic activity. The drug, therefore, is of little value when used alone. It is used in combination with more potent drug such as isoniazide (INH).

Mechanism of action : Lehmann's original principle leading to the discovery of PAS furnished mechanism of action to be proposed for the drug. It assumes that benzoates and salicylates are important metabolites within

tubercle bacilli and PAS exerts its effect by interfering with their utilization.

Toxicity : Severe toxic reactions are rare. Agranulocytosis, allergic reactions and crystalurea have been reported. Gastrointestinal irritation with vomiting and diarrhoea may occur but can be controlled by aluminium hydroxide and atropine.

2. Thiacetazone :



(1)

The development of thiosemicarbazones came about because of the continuing interest of Domagk and his collaborators in the sulfonamides and sulfones.⁵ The thiosemicarbazones are condensation products of carbonyl compounds with thiosemicarbazide. A large number of these compounds have been prepared and tested for antituberculous activity in vitro and in vivo. The most active of these compounds is 4-acetamidobenzaldehyde thiosemicarbazone (1) now referred to as thiacetazone/amithiazone.⁶

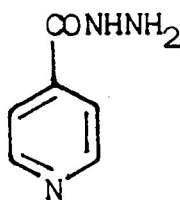
It is used in low doses, as a cheap substitute for

PAS in combination with INH. The usual recommended dose of the drug is 150 mg (2 mg/kg) daily in a single dose given with INH.

Mechanism of action : Actual mechanism of action is not known. Liebermeister⁷ established that thiacetazone, forms a copper complex and this complex resembles the actual biochemical carrier of the copper and interfere with their function.

Toxicity : The major limitation to the use of thiacetazone, arises from the marked toxicity which occurs when therapeutic doses are employed. Patients may acquire damage to the liver, kidneys and bone marrow.⁸ Drug resistant strains also develop rapidly during therapy.

3. Isoniazide (INH) :



Isoniazide (isonicotinic acid hydrazide, INH) was first described as a chemical substance in 1912.⁹ Its activity in tuberculosis was not known until 40 years later, when it was rediscovered by research teams of three major pharmaceutical laboratories.¹⁰⁻¹² Each of these teams was working on the modification of thiosemicarbazones

in an attempt to increase the antitubercular activity. Because of the tuberculostatic activity of nicotinamide, the pyridine nucleus was a prominent candidate to be incorporated in new agents. Among other pyridine aldehyde thiosemicarbazone synthesized, isonicotinic aldehyde thiosemicarbazone was one compound. It was prepared using isonicotinic acid hydrazide as starting material. Since antitubercular testing of chemical intermediates was routine in these laboratories, the remarkable activity of INH was quickly recognized.

Mechanism of action : The voluminous literature on this subject is available. Various theories were proposed for this. There are number of theories which involve in some way, the affinity of isoniazide for metals or metalloporphyrines (hemin, catalase, etc.). The molecule is a powerful chelator of metals and because of the nature of the hydrazine portion, it is capable of reducing certain metal ions, free or complexed. The simplest of these theories asserts that isoniazide is bacteriostatic because it complexes essential metals such as copper or iron. In this way it would interfere with the function of important oxidation-reduction enzymes that employ these metals. But this theory does not explain why closely related hydrazides, which complex metals equally well or better, do not show comparable antitubercular activity.

Another set of mechanism of action was suggested to its originators because of the great chemical similarity of isoniazide to the nicotinamide in dehydrogenase cofactors, nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate (NAD and NADP respectively, coenzyme I and coenzyme II). One of these theories assumes that isoniazide in mycobacteria is converted to isonicotinic acid, which can replace the nicotinamide of NAD to form nicotinic acid analogs of NAD. This analog then disturbs the NAD and NADP dehydrogenases.¹³

Some other proposed action mechanisms for INH are -

1) Pigment production by sensitive mycobacteria invariably accompanies isoniazide treatment.¹⁴ Accumulation of toxic pigments might account for inhibition.

2) INH reacts readily with pyridoxal. It has been proposed that depletion of this essential material is the basis of the effect of INH on mycobacteria.

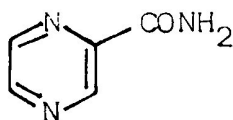
3) inhibition of synthesis of mycolic acid has been proposed as the primary action of isoniazide.¹⁵ This inhibition is a prominent feature of the action of isoniazide on the cell wall of mycobacteria. The mycolic acids are major constituents of the cell walls of these

Mycobacteria and are unique to them. Inhibition of the synthesis of mycolic acids by isoniazide, therefore, explains the high specificity of isoniazide for mycobacteria.

Several chemical theories supporting the isoniazide action have been explained. The validity of any one of these is at the moment uncertain.

Toxicity : In large doses, INH inhibits the glutamic acid decarboxylase of brain by combining with and then removing its coenzyme pyridoxal phosphate. The brain concentration of γ -aminobutyric acid is thereby reduced and convulsions result. In therapeutic doses, peripheral neuritis is the main toxic symptom, which is due to the pyridoxine deficiency. This can be controlled by daily administration of vitamin B₆. Other toxic symptoms are minor and include constipation, difficulty in starting micturition, hypotension, eosinophilia, slight anaemia and albuminuria.

4. Pyrazinamide :



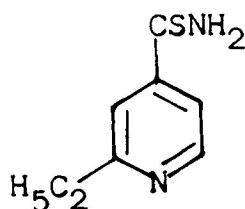
Pyrazinamide was first used in experimental tuberculosis in 1952 as a result of independent research in different laboratories.¹⁶⁻¹⁸ It had been synthesized 15 years previously as a chemical intermediate.¹⁹ The antituberculous activity of nicotinamide had been discovered in 1945 and later independently in 1948.^{20,21} The preparing and testing of compounds bearing a structural resemblance to nicotinamide led to pyrazinamide.¹⁶⁻¹⁸

Mechanism of action : The mechanism of action of pyrazinamide is not definitely known. Its resemblance to nicotinamide has led to the suggestion that pyrazinamide affects nicotinamide or nicotinic acid metabolism.²⁰ The effectiveness of pyrazinamide could be due to interference in some way with the role of nicotinamide (or nicotinic acid) as a cofactor in the dehydrogenases.

Toxicity : Most patients complain of a metallic taste and sulfurous eructations. Apart from arthralgia, anorexia, nausea, vomiting malaise, mild skin rashes and rarely photosensitivity resulting in bright red-brown discolouration of the exposed parts of the body. The serious toxic effects involve the liver. Toxic hepatitis may occur at any time during the course of treatment as early as 7th day and as late as the 8th month.

Combination of streptomycin, INH and pyrazinamide is highly effective regime. When the drug is used alone, resistance develops within 8 to 12 weeks.

5. Ethionamide :



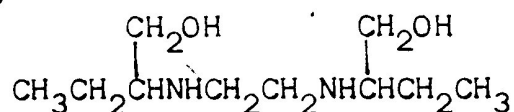
This compound was prepared for tuberculosis testing by Libermann and colleagues.²¹ Its antituberculous activity is described by Rist and co-workers.²² Ethionamide was synthesized to further improve antituberculous activity of compounds arising from chemical manipulation of the structural elements of thioureas and thiosemicarbazones.

Mechanism of action : Ethionamide is cross-resistant to thioureas and thiosemicarbazones, which means that probably these substances share a common mode of action. Ethionamide is easily converted to a substituted isonicotinic acid in the cell. The isonicotinic hypothesis for action of isoniazide has been extended to ethionamide.²³

Toxicity : Toxic effects are minor, consisting chiefly of gastrointestinal distress and anorexia. Postural hypotension, drowsiness and impotence occur less frequently,

as does liver damage, which may be the result of sensitivity to the drug.

6. Ethambutol :



The high antitubercular activity of the ethambutol was announced in 1961 by Wilkinson and associates.^{24,25} It was developed in a rational synthetic programme which was began with the knowledge that related diamines had slight antituberculous activity because of their ability to chelate metal ions.

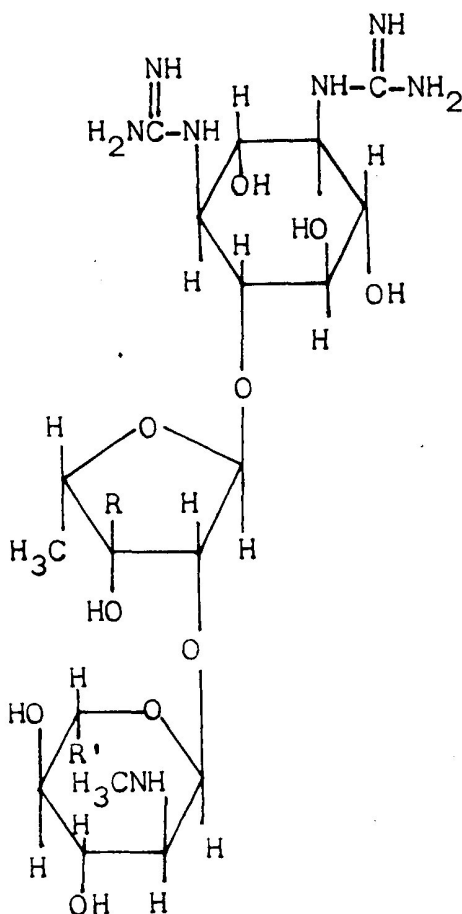
Ethambutol is the dextrorotatory isomer of 2,2'-(ethylene diamine)-di-1-butanol. The levarotatory form is inactive against the mycobacteria but is equally toxic.

Mechanism⁰ of action : The mechanism of action of ethambutol is not precisely known. Inventors of ethambutol followed metal chelation principle while developing it from diamines.²⁶ But ability to form chelate is not enough to insure antitubercular activity, because several closely related compounds capable of chelating metals equally well, are inactive. Therefore, it was postulated that ability to form a metal chelate must occur simultaneously with the ability of the compound (or its chelate) to fit a specific enzyme template.

Toxicity : Resistance to the drug develops rapidly. It is used in combination with other antitubercular drugs. It might be substituted for PAS in the initial treatment of the disease. The most serious toxic effects are on vision. There is decrease in visual acuity and loss of green-red perception suggests retrobulbar neuritis.

ANTIBIOTICS

7. Streptomycin :



Streptomycin : $R = \text{CHO}$, $R' = \text{CH}_2\text{OH}$.

Dihydrostreptomycin : $R = \text{CH}_2\text{OH}$, $R' = \text{CH}_2\text{OH}$.

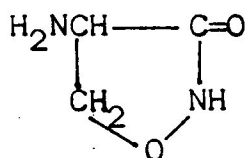
The isolation of streptomycin from a culture of Streptomyces griseus was first shown by Schatz et al.²⁸ The inhibitory effect of this substance in vitro on Mycobacterium tuberculosis was first announced by Schatz and Waksman (1944).²⁸ It is an organic base which forms water soluble salts. The base and the salts in a dry state are stable at room temperature. Dihydrostreptomycin, a related compound, is more stable than streptomycin, but because of its property to produce irreversible auditory damage, it is not commonly used in therapeutics.

Mechanism of action : Fitzgerald et al.²⁹ showed that streptomycin inhibits enzyme induction in nondividing cells of mycobacterium. This suggested inhibition of protein synthesis. According to another hypothesis, streptomycin induces the ribosomes to manufacture peptide chains with wrong amino acids which ultimately destroy the bacterial cell. In addition, variety of enzymes diamine oxidase, xanthine oxidase and others involved in Kreb's cycle are inhibited by streptomycin. These effects contribute to, but are not essential to the bactericidal action.

Use and toxicity : It should be used with caution in elderly, 0.75 g daily is considered the preferred regime in such patients. When used alone, permanent bacterial

resistance develops in 3 to 5 months. It produces usual allergic reactions, in sensitive patients. Erythema, rashes, urticaria and purpura, may occur as may a fall in blood pressure accompanied by headache, nausea, and vomiting. Large dose may cause albuminuria and liver damage. The specific toxicity is manifested by damage to the eighth nerve and labyrinth, symptoms of which appear after 2 or 3 weeks of therapy. Following prolonged therapy deafness may occur.

8. Cycloserine (Seromycin) :



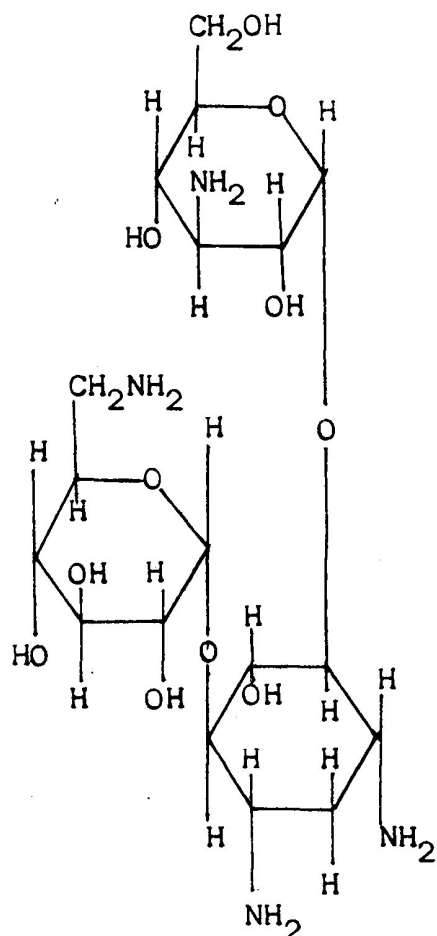
Cycloserine is the antibiotic, which was discovered in several laboratories independently and simultaneously. It was isolated by Harned et al.³⁰ from Streptomyces orchidaceus and Strep. garyphalus.

Mechanism of action : This compound can be considered as a cyclic derivative of D-alanine. Strominger et al.^{31,32} showed that, it interferes with cell wall synthesis but at a different locus from penicillin.

Toxicity : Use of this drug is limited by its toxicity. The neurological effects include muscular

weakness, tremor, increased reflexes, ataxia, slurred speech and convulsions.

9. Kanamycin :

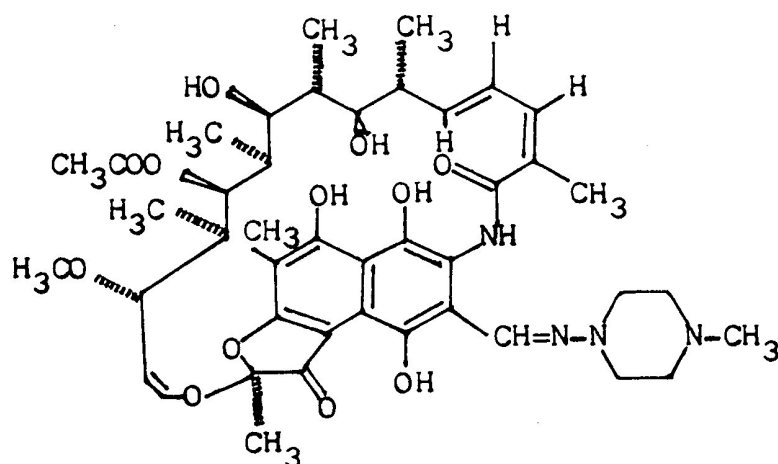


It was isolated by Umezawa et al.³³ in 1957 from a soil organism Streptomyces kanamycetis. It can be isolated from fermentation beer by adsorption on cation resin and purified by repeated elution and re-adsorption on resin.

Mechanism of action : The mode of action of kanamycin is similar to that of streptomycin and other amino glycoside antibiotics as it interacts with 30 S ribosomal subunits, inhibits protein synthesis and causes misreading of the genetic code.

Toxicity : It produces vertigo and deafness. It causes less vestibular but more auditory damage than streptomycin. After prolonged use it produces eighth nerve and renal damage.^{34,35}

10. Rifampicin :



It is a semisynthetic derivative of rifamycin B, isolated from Streptomyces mediterranei.³⁶ It is very active against mycobacteria, resistant to the standard chemotherapeutic agents and against majority of atypical mycobacteria.

This compound was isolated from Streptomyces puniceus in 1951 by Mayer et al.³⁸ and Bartz et al.³⁹ It is a basic polypeptide containing guanidine. The sulfate salt is stable in the dry state and soluble in water.

Mechanism of action : Mode of action of viomycin resembles that of the amino glycoside (as streptomycin). It inhibits protein synthesis by binding to ribosomes as do the amino glycosides.

Toxicity : Renal damage, casts, electrolyte unbalance (excess K^+ and Ca^{++} excretion in the urine) and albuminurea may occur even when minimal effective doses are used, but they disappear when drug is withdrawn.

12. Capreomycin :

It was isolated by Herr et al.⁴⁰ from Streptomyces capreolus. It is a mixture of capreomycins IA, IB, IIA, IIB, their relative proportions are 25, 62, 3 and 6 percent, respectively.

Mechanism of action : Tubercle bacilli resistant to capreomycin are also resistant to viomycin, that is, cross resistance exists. This shows that viomycin and capreomycin may have same mode of action.

Toxicity : Toxicity thus far has been minimum. Slight renal damage and a few cases of deafness have been reported. It should be administered with caution in the presence of renal impairment. It should not be combined with streptomycin, kanamycin or viomycin.



PLAN OF WORK



PLAN OF WORK

Of all the infectious diseases that have plagued man, tuberculosis has probably been the most responsible for the greatest morbidity and mortality in human beings. It has apparently plagued man ever since human beings emerged as a species on this planet. Its depredations, especially over the last several hundred years have earned it the epithet, "The captain of all men of death".⁴¹ It is a major health problem in developing countries, where 30-60 % of adults are infected with Mycobacterium tuberculosis. Approximately 8-10 million individuals develop clinical tuberculosis (T.B.) and 3 million die of T.B. each year.

Attempts to find suitable chemotherapeutic agents for tuberculosis were started from the time, of the Koch (1882). The modern chemotherapeutic era began when Rich and Follis in 1938 established that sulfanilamide exerts a slight suppressive effect on experimental tuberculosis in guinea pigs. Since that time, numerous investigators have attempted to find chemotherapeutic agents suitable for the treatment of tuberculosis and their efforts have been rewarded by discovery of streptomycin, p-amino salicylic acid, isoniazide and variety of other clinically useful but less effective drugs. None of these, however, either

alone or in combination gave a satisfactory therapeutic results because inspite of intensive chemotherapy, tubercle bacilli may persist in the tissues or in lesions for longer period of time. Therefore, it becomes essential to search for more new erradicative drugs.⁴²

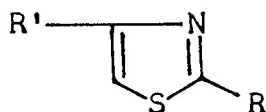
With above view in mind, it was planned to synthesise different types of organic compounds, as explained in the various sections included in this chapter.

Section - A

2-(Alkyl/substituted phenyl/heterocyclic)-4-(N,N-diethyl-N'-phenyl urea)thiazole :

Thiazole derivatives have significant chemotherapeutic activities.⁴³ Compounds, such as vitamin B, sulphathiazole, promizole, niridazole, aminitrazole, thiabendazole, tetramisole, all contain thiazole ring in one form or another.

Recently Prabhu et al.⁴⁴ have reported that 2,4-disubstituted thiazoles (I) have shown good response against tubercle bacilli.

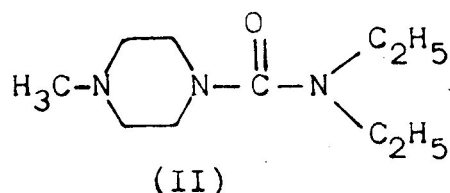


(I)

R = Alkyl, aryl; R' = 2-pyrazinyl, 5'-nitro-2'-furyl, 1-adamantyl.

These compounds were active against M. tuberculosis in range 0.39 µg/ml to 200 µg/ml.

N,N-Diethyl carbamazine (Hetrazan) is a well known marketed drug, used for its antifilarial activity.



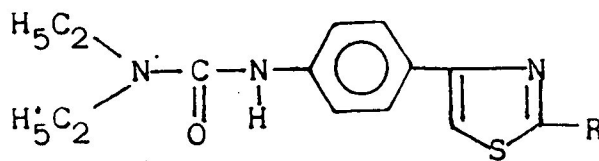
Its activity is mainly due to N,N-diethyl carbamoyl linkage. 45

Similarly, N,N-diethyl carbamoyl derivatives of substituted anilines, heterocyclic amines and bis-aryl-amines were prepared in our laboratory. Some of these compounds were found active against rodent malarial strain Plasmodium berghei in mice.

Taking into consideration the facts about N,N-diethyl carbamoyl and the biological active thiazole; it was planned to synthesise 2-(substituted-aryl/heterocyclic)-4-(p-amino phenyl) thiazole and incorporate N,N-diethyl linkage into it.

Thiazole moiety was prepared by reaction between substituted thioamides and ω-chloro-p-amino acetophenone. Totally ten compounds have been synthesized in this series.

All these were tested for in vitro antitubercular activity against H₃₇Rv strain of M. tuberculosis. The general structure of these thiazole compounds is as shown (III).



(III)

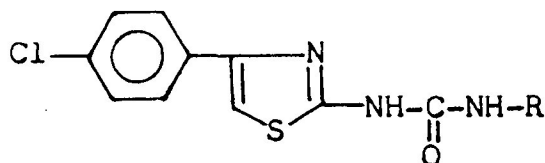
where, R = Methyl, substituted-aryl, heterocyclic, etc.

Section - B

2-(Substituted anilino/heterocyclic amino)-4-(N,N-diethyl-N'-phenyl urea) thiazole :

During literature survey it was found that substitution of amino group at 2 position and substitution of phenyl ring at 4 position of thiazole ring impart bacteriostatic activity to it.

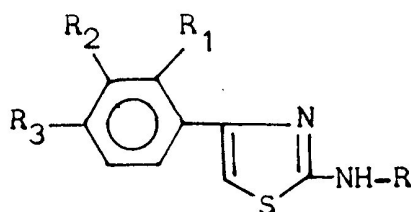
Among the various substituted thiazole derivatives Priscot, Petric R. patented 1-[4-(monohalophenyl)-2-thiazolyl]-3-urea (IV) as good nematocides.⁴⁶



(IV)

where, R = Methyl.

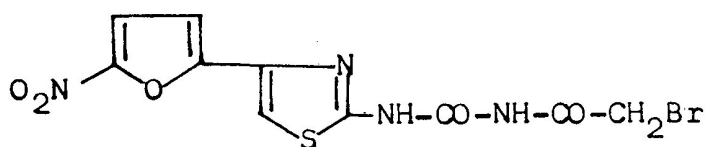
Recently, substituted thiazoles are reported as antiviral chemotherapeutic agents. Among them Grafe et al. reported 4-substituted-phenyl-2-substituted amino thiazoles as antiviral agents.⁴⁷ (V).



(V)

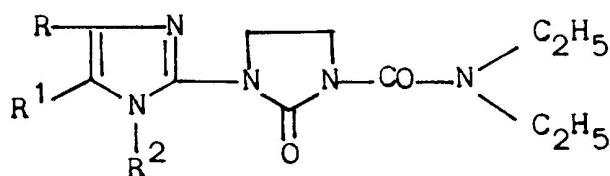
where, R = H, Me, Pr; R₁ = H, Me; R₂R₃ = H, Cl, OMe.

Closier et al.⁴⁸ from Park-Davis Company, England, while synthesizing different 2,4-disubstituted thiazoles succeeded in obtaining compound (VI) with highest in vitro antibacterial activity, against Streptococcus aureus and M. tuberculosis at 0.08 µg/ml and 20 µg/ml, respectively.



(VI)

2-Imidazolidione imidazole (VII) when substituted with N,N-diethyl carbamoyl linkage has shown bactericidal, protozoacidal and schistosomacidal activity.⁴⁹



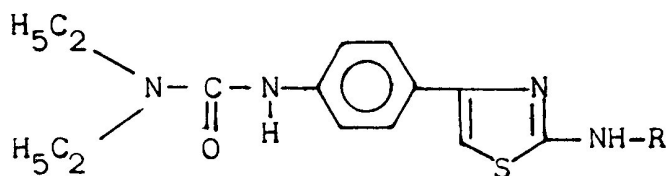
(VII)

R, R¹ = H, lower alkyl, and -NO₂;

R² = Lower alkyl, amino alkyl, etc.

Considering above experimental findings, it was thought worthwhile to exploit the antitubercular effect of 2-substituted-amino-4-(p-aminophenyl) thiazole along with N,N-diethyl carbamoyl linkage.

About fourteen compounds having following general structure were synthesized (VIII).



(VIII)

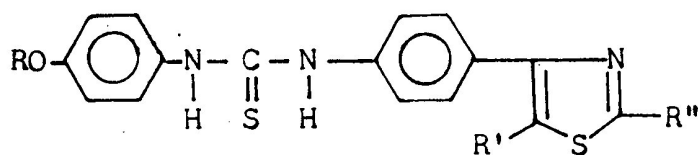
R = Substituted-phenyl, substituted-heterocyclic, etc.

These compounds were prepared by condensing different monosubstituted thioureas (aryl/heterocyclic) with p-aminophenyl haloketone. Then reacting N,N-diethyl carbamoyl chloride with free amino group on phenyl ring at position 4 of thiazole molecule. All these compounds were subjected for in vitro antitubercular screening.

Section - C

2-(Substituted-anilino/heterocyclic amino)-4-(N,N-diethyl-N'-phenyl urea)-5-methyl thiazole :

Kulkarni et al.⁵⁰ while studying structure activity relationship of thiazolyl thiocarbanilides (IX) found that compounds containing no substitution in thiazole ring were less active as antitubercular. The activity



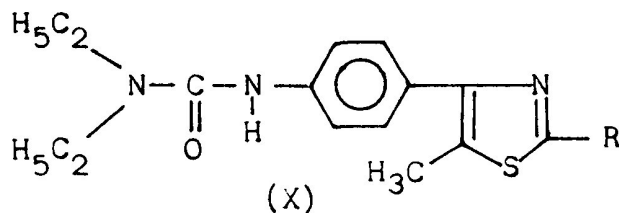
(IX)

where, R = CH₃, C₂H₅, *n*-C₃H₇ ; R' = H, CH₃ ;

R'' = H, CH₃, *n*-iso-C₄H₉.

increased with the introduction of methyl group in the ring. It was noted that 5-methyl derivatives were more active than corresponding 2-methyl derivatives.

Hence, it was thought of interest to incorporate methyl group at position 5 of the 2-(substituted anilino/heterocyclic amino)-4-(*p*-amino phenyl) thiazole along with the N,N-diethyl carbamoyl linkage at 4 position (X).



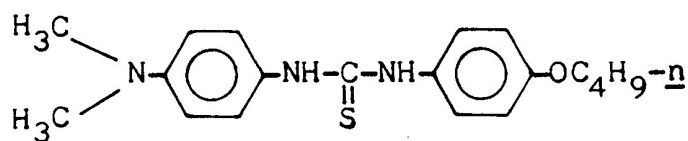
R = Substituted-anilino/heterocyclic amino, etc.

The thiazole nucleus was synthesized by reaction between ω -chloro-*p*-amino propiophenone and various mono-substituted phenyl/heterocyclic thioureas. Fourteen such compounds prepared in this series were screened for their in vitro antitubercular activity.

Section - D

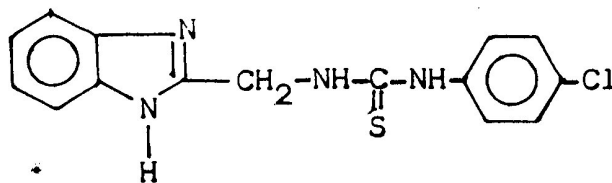
p-(Butyl)-*p'*-[4-(2,5-disubstituted)thiazolyl]-thiocarbanilide :

Thiourea derivatives have been found to possess wide therapeutic activities.⁵¹ Substituted thiourea derivatives are known for antitubercular,⁵² antileprosy⁵³ and antimalarial⁵⁴ activities, e.g., thiambutasine (XI) is a thiourea derivative and is very effective against *M. tuberculosis* and *M. leprae*.⁵⁵



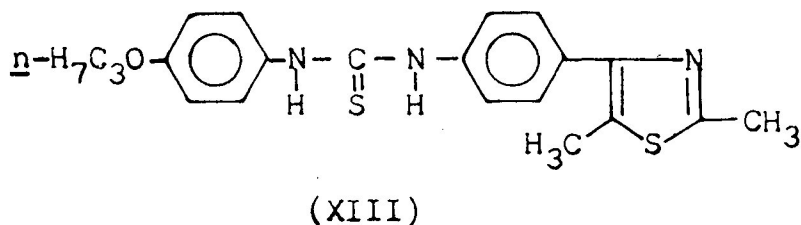
(XI)

Benzimidazol-2-yl methyl thioureas (XII) are found active as antimicrobial.⁵⁶

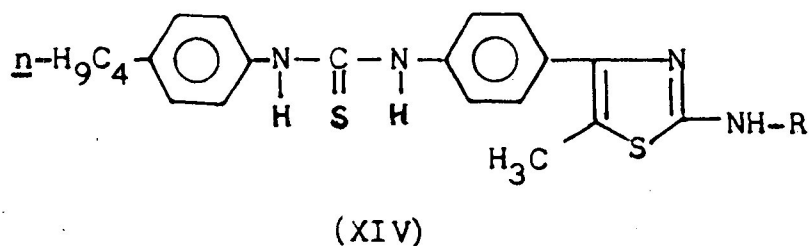


(XII)

A substituted thiocarbanilide (XIII) incorporating a thiazole moiety was reported to show in vitro activity against M. tuberculosis at concentration 0.04 $\mu\text{g/ml}$.⁵⁰



With this example in mind, above literature observations and previous findings about active thiazole moiety, having substituted amino group at position 2 and phenyl group at 4 position, we thought it of interest to synthesise p-(butyl)-p'-[4-(2,5-disubstituted)thiazolyl]-7-thiocarbanilides (XIV).



R = Substituted-phenyl, heterocyclic, etc.

These compounds were synthesized by condensation of p-butyl-phenyl isothiocyanate and 2-(substituted-anilino/heterocyclic amino)-4-(p-aminophenyl)-5-methyl thiazole.

Totally fourteen compounds have been synthesized and have been screened for their in vitro antitubercular activity.

SECTION - A

* CHEMISTRY OF THIOAMIDES

* EXPERIMENTAL

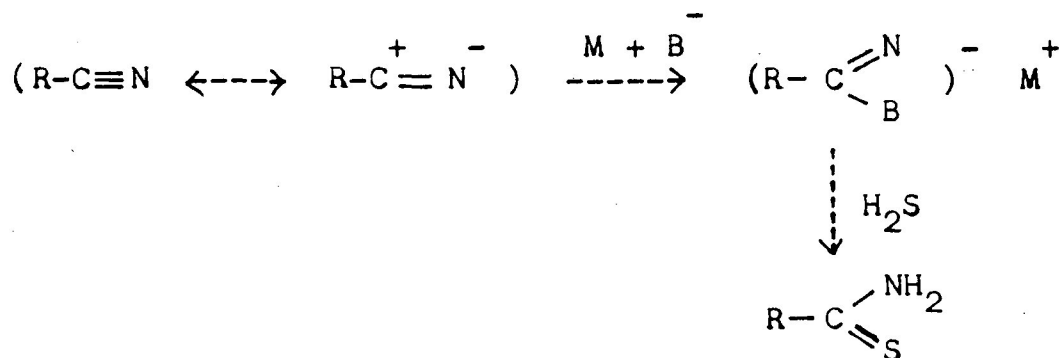
CHEMISTRY OF THIOAMIDES

The chemistry of thioamide has been developing rapidly for last 25 years because of its use as herbicidal and as pharmacologically important substances.

Synthetic methods of thioamides :

1. Reactions of nitriles with hydrogen sulphide :

The synthesis of thiocarboxamides from nitriles is one of the oldest method. The reaction requires high hydrogen sulfide concentration. It is catalysed by bases,^{57,58} and is generally favoured by exclusion of water. The base catalysed addition of hydrogen sulfide to nitriles can be illustrated as below :

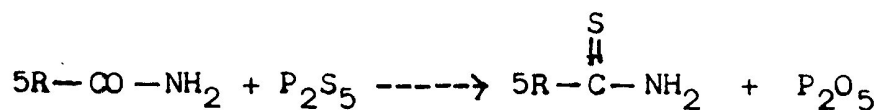


Suitable catalysts, apart from ammonia include aliphatic amines, pyridine, alkoxides and potassium hydrogen sulfide.^{59,60}

Fairfull et al.⁶¹ obtained very good yields by addition of hydrogen sulfide to aromatic nitriles in the presence of pyridine and triethylamine.

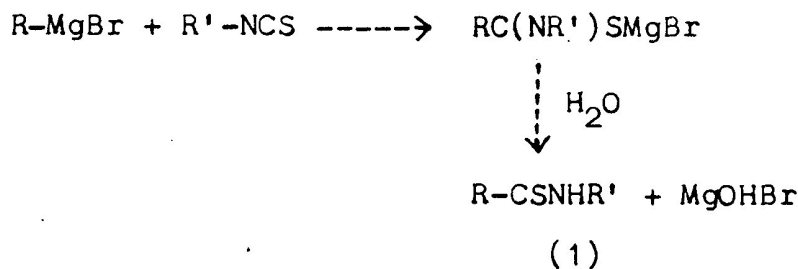
2. Sulphurization of amides :

The replacement of the oxygen in carboxamide, by sulfur is a general method for the preparation of thio-carboxamides. The most useful reagent for this replacement is phosphorus pentasulfide.⁶² It was also found that presence of potassium thiophosphate along with phosphorus pentasulfide enhanced the yield of final thioamides.⁶³



3. Addition of nucleophiles to isothiocyanates :

Isothiocyanates react with Grignard reagents and subsequent hydrolysis under mild conditions leads to thiocarboxamides (1).



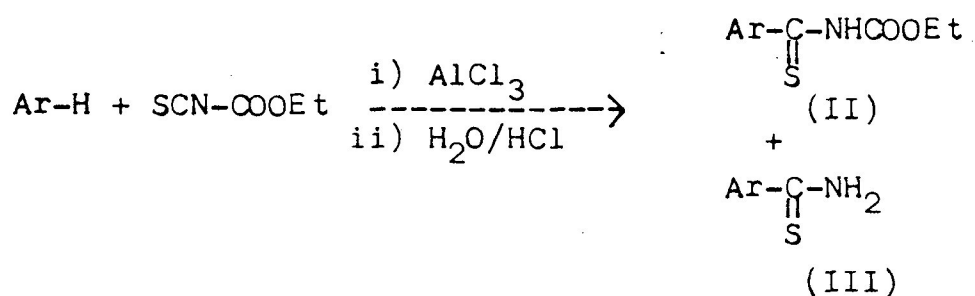
This method was first used by Sachs and Loevy,⁶⁴

Worral⁶⁵ later used it to prepare a large number of N-substituted thiovaleramides. A number of thiocarboxamides can be obtained by this method, e.g., $\text{H}_9\text{C}_4\text{-CS-NH-C}_6\text{H}_4\text{-CH}_3\text{O}$ in 100 % yield.

4. One step synthesis of aromatic thioamides :

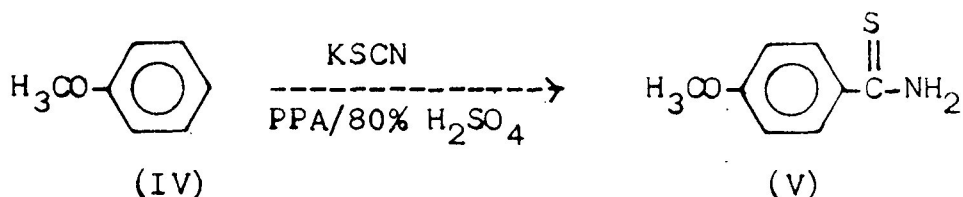
a) Friedel-Craft's thioacylation with ethoxy carbonyl isothiocyanate :

It has been found⁶⁶ that ethoxy carbonyl isothiocyanate reacts readily with various aromatic compounds in presence of anhydrous aluminium chloride. However, depending upon the conditions, it either yields the expected N-ethoxy carbonyl thioamide (II) or thioamide (III) itself.



The nature of the product appears to be controlled mainly by two factors, the quantity of catalyst and the reaction temperature. For thioamide to be the major product, a molar ratio of AlCl_3 to isothiocyanate equal to at least 2:1 must be maintained. Low reaction temperature favours the N-ethoxy carbonyl thioamide.

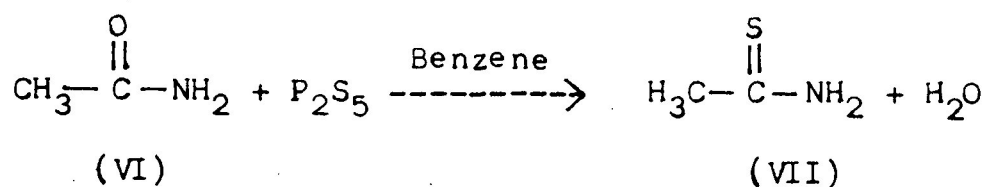
b) Aryl thioamides (V) can also be prepared by heating phenolic ether such as anisole (0.01) (IV) or veratrol at 60°C in presence of polyphosphoric acid (PPA) or 80% H₂SO₄ with potassium thiocyanate⁶⁷ (0.01 mole).



In case of PPA, thioamides were obtained in 50% yields, while, yields were increased by 5-10 % if 80% H₂SO₄ is used instead of PPA.

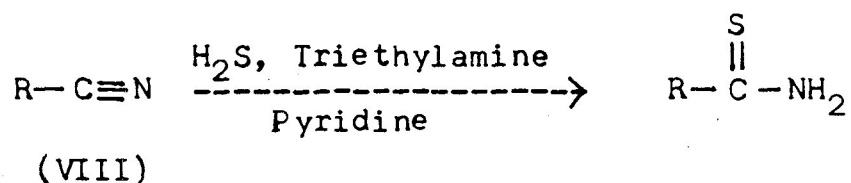
In present research work, ten various types of thioamides, such as (i) thioacetamide, (ii) thiobenzamide, (iii) substituted phenyl thioamide, (iv) pyridyl thioamides, and (v) substituted phenoxy acetothioamides as shown in Table 1 were synthesized.

Thioacetamide (VII) was prepared by reacting acetamide (VI) (1.0 mole) in dry form with pure phosphorus pentasulfide (0.225 mole) in sodium dried benzene with 21% yield.



Dry condition gives good yield for this reaction.

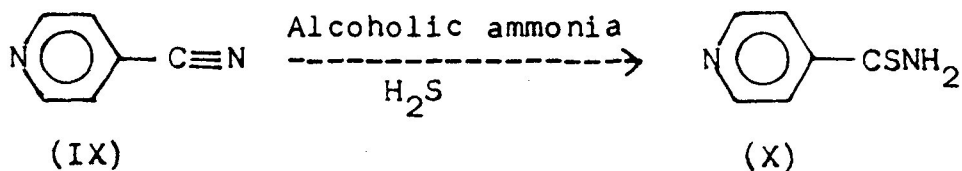
Thiobenzamide, substituted-phenyl thioamides and substituted-phenoxy acetothioamides were prepared by reacting appropriate nitriles (VIII) with dry gaseous hydrogen sulfide in pyridine in presence of triethylamine (TEA) as base catalyst.



where, R = Phenyl, substituted-phenyl,
substituted-phenoxyaceto.

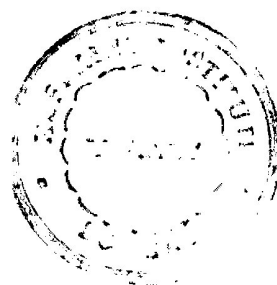
The basic conditions maintained during reaction give yields in the range of 50 to 90 %.

In case of 3-pyridyl or 4-pyridyl thioamides (X) the above procedure was not found satisfactory as far as their yields are concerned. Hence, these thioamides were prepared by heating 3-cyanopyridine or 4-cyanopyridine (IX) saturated with H₂S in presence of alcoholic ammonia, in closed reactor under pressure in 60 and 71% yields, respectively.



.....

EXPERIMENTAL

EXPERIMENTALSYNTHESIS OF THIOAMIDES1) Thioacetamide :

In a 500 ml round bottomed flask equipped with a condenser, guard tube, was placed pure dry acetamide (29.5 g; 0.5 mole), phosphorus pentasulfide (12.45 g; 0.056 mole), sodium-dry benzene (100 ml) and it was refluxed for two hours. The hot benzene layer was decanted and the syrupy residue was extracted 4 to 5 times with 25 ml portions of boiling benzene. The combined extract was dried and filtered. The filtrate was treated with charcoal, filtered and concentrated. The filtrate, on cooling gave yellow crystals of the product. It was filtered, washed with little benzene and air-dried.

Yield : 8.7 g (23.2 %); m.p. 106-107°C.

(Lit.⁶¹ m.p. 107-108°C).

2) Thiobenzamide :

In a 100 ml conical flask, was taken benzonitrile (11.7 g; 0.1 mole), pyridine (20 ml) and triethylamine (10.1 g; 0.1 mole). Dry hydrogen sulfide gas was passed for six hours at room temperature in a steady flow through above reaction mixture. Then reaction mixture was poured on water with stirring. The solid product obtained was

filtered, washings of cold water were given and dried.

Thiobenzamide, so obtained was crystallized from benzene to get yellowish crystals.

Yield : 8.8 g (58.39 %); m.p. 115-116°C
(Lit.⁶⁰ m.p. 116°C).

Benzyl thioamide, *p*-methoxyphenyl thioamide, 3-methoxy-4-propoxyphenyl thioamide, 5-bromovanillin thioamide, 2,3-dichlorophenoxy acetothioamide, 4-N,N-dimethyl amino thiabenzamide were prepared from the corresponding nitriles following the procedure used for the preparation of thiobenzamide from benzonitrile.

3) 3-Pyridyl thioamide :

In a stainless steel pressure vessel was taken 3-cyanopyridine (6.0 g; 0.057 mole) in absolute ethanol (15 ml). The vessel was cooled in freezing mixture and dry hydrogen sulfide gas was bubbled into it till saturation. The vessel was closed tightly and heated on steam bath for two hours. After cooling down to room temperature, the vessel was opened carefully and the contents were evaporated to dryness. The crude thioamide thus obtained was crystallized from benzene to get pure product.

Yield : 5.75 g (73.1 %); m.p. 180°C.
(Lit.⁶⁰ m.p. 180-181°C).

4-Pyridyl thioamide was prepared from 4-cyano-pyridine following the procedure same as above.

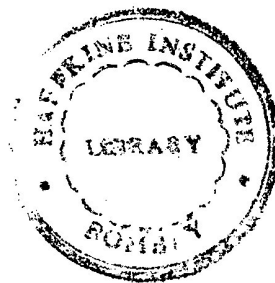


TABLE-1 : ThioamidesR CSNH₂

No.	R	Mol. formula	M.p. ^{°C} Found	M.p. ^{°C} Reported	REFERENCE
1.	Methyl	C ₂ H ₅ NS	106-108	107-108	62
2.	Phenyl	C ₇ H ₇ NS	115-116	116	61
3.	Benzyl	C ₈ H ₉ NS	96	97	61
4.	p-Methoxyphenyl	C ₈ H ₉ NOS	148-149	149	61
5.	3-Methoxy-4-propoxy-phenyl	C ₁₁ H ₁₅ NO ₂ S	127-128	128-129	68
6.	Bromovanillino	C ₈ H ₈ BrNO ₂ S	180-181	-	- *
7.	2,3-Dichlorophenoxy-aceto	C ₈ H ₇ Cl ₂ NOS	160-161	-	- *
8.	N,N-Dimethylamino-phenyl	C ₉ H ₁₂ N ₂ S	255	256	70
9.	3-Pyridyl	C ₆ H ₆ N ₂ S	180-181	183	61
10.	4-Pyridyl	C ₆ H ₆ N ₂ S	202-203	203-204	69

* Obtained from laboratory.

SECTION - B

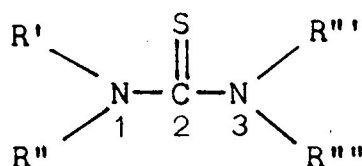
* CHEMISTRY OF THIOUREAS

* EXPERIMENTAL

CHEMISTRY OF THIOUREAS

Synthesis of monosubstituted thioureas :

Thioureas, in general, are well defined crystalline compounds of high stability. Structure of thiourea is generally represented as shown below :



The main part of chemistry of thioureas consists of reactions, due to their nucleophilic reactivity. The centre of reaction is located either at nitrogen atom or at sulfur atom. Substitution at single nitrogen gives 1-monosubstituted, whereas, substitution at both nitrogen atoms gives 1,3-disubstituted derivatives of thioureas. The S-substituted thioureas are referred as pseudothioureas.

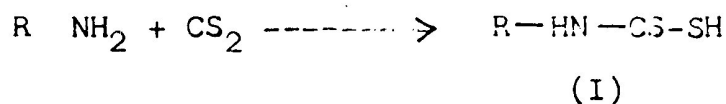
There are several synthetic methods known for preparation of thiourea derivatives. Many variations have been applied to each of these when circumstances demanded it.

In this chapter synthesis of monosubstituted-thioureas is discussed.

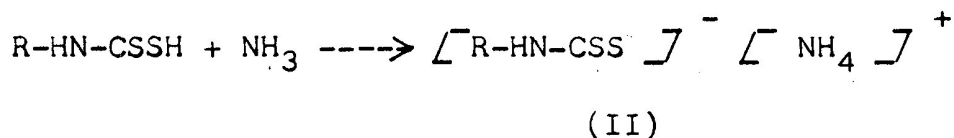
General methods for the preparation of 1-mono-substituted thioureas⁷⁶ are -

(A) Reaction between carbon disulphide amines :

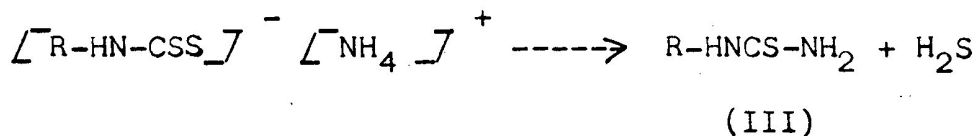
The reaction between carbon disulfide and primary/secondary/aliphatic or aromatic amine gives dithiocarbamic acid (I) at room temperature.



Dithiocarbamic acid when reacted with molar proportion of ammonia, gives ammonium dithiocarbamate (II).

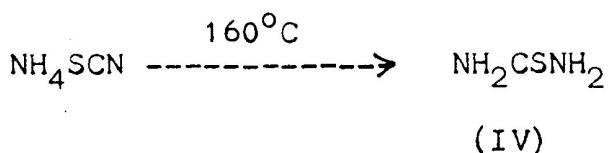


This salt of monosubstituted dithiocarbamate on heating gives 1-monosubstituted-thiourea (III).

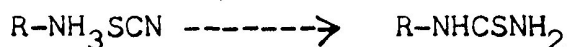


(B) Action of alkali thiocyanate on amine hydrochloride :

It has been known that heating ammonium thiocyanate at 160°C for several hours causes it to rearrange to thiourea (IV).



The same rearrangement occurs when the ammonium ion is mono or disubstituted, but not when it is tri- or tetrasubstituted. Use of this rearrangement is made, in preparing 1-monosubstituted thioureas.

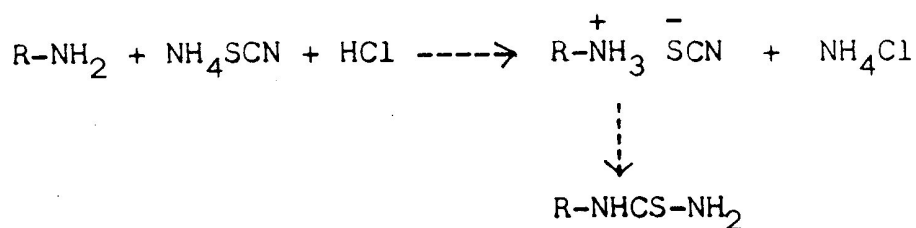


The reaction can be carried out in either -

- (a) an inert organic solvent, or
- (b) aqueous medium.

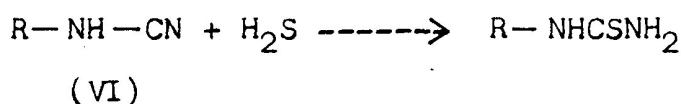
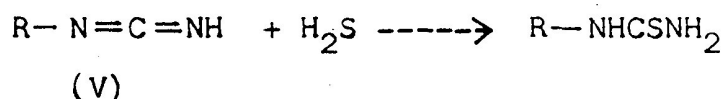
a) Chlorobenzene is commonly used as a solvent. It is saturated with hydrogen chloride and the amine and thiocyanate are added. The mixture is then heated at 110-120°C. Organic salts are removed by filtration, and the product is isolated from the filtrate.

b) One mole of the amine is dissolved in water containing 1.3 moles of hydrogen chloride. Ammonium thiocyanate is added and after a reflux period the solution is evaporated to dryness on a steam-bath. The residue is heated for several additional hours, taken up in benzene and washed with dilute hydrochloric acid. Evaporation of the dried benzene layer yields the product.



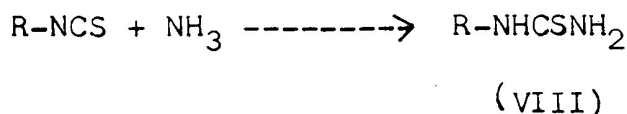
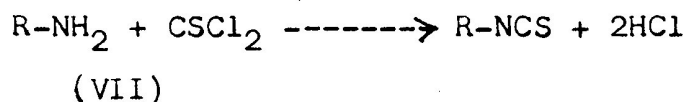
(C) Thiohydrolysis of cyanamide and carbodimides :

This method is based on the ability of carbodimides (V) and cyanamides (VI) to add H_2S .



(D) Organic isothiocyanates and ammonia :

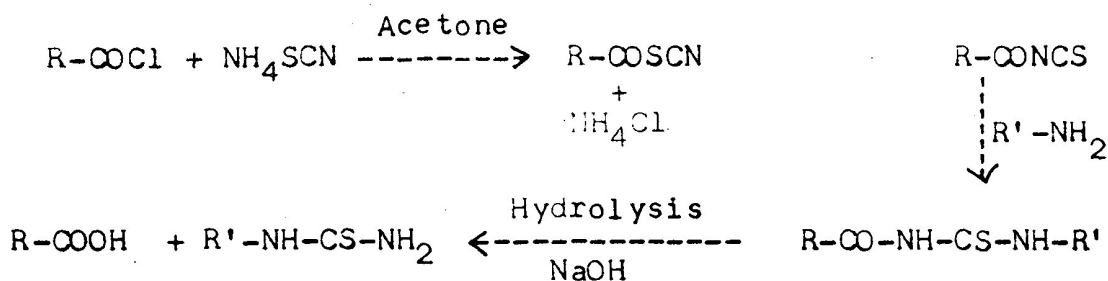
Primary amines react with thiophosgene (VII) to give an isothiocyanate, which reacts with ammonia to give corresponding thioureas (VIII).



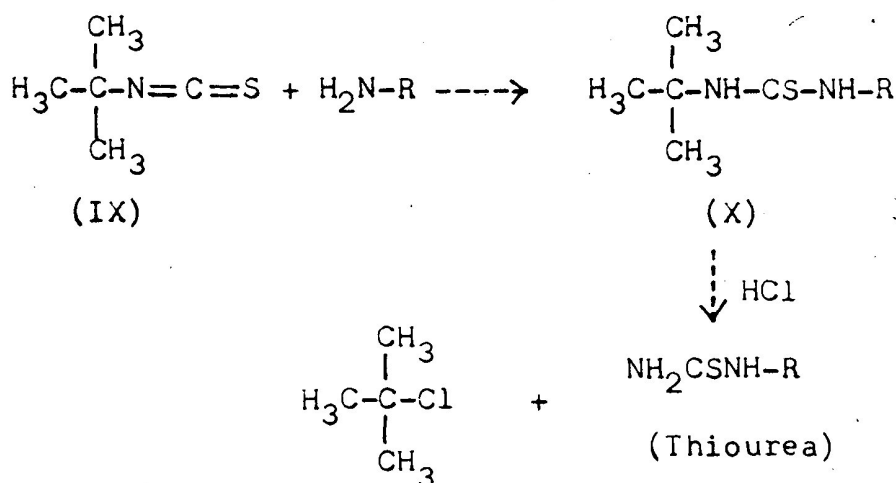
For the preparation of 1-amino-substituted thioureas, not a single method of general application is known.

The available method that is, isomeric change of amine isothiocyanate into corresponding 1-monosubstituted-thioureas is applicable only to aromatic primary amines and on limited basis to aromatic and mixed secondary amines.⁷¹⁻⁷⁴ The reaction of ammonia with isothiocyanates is restricted in measure, because the isothiocyanates can not be prepared very easily.⁷⁵ The use of thiophosgene is very much restricted by its being expensive and toxic in nature. Also isothiocyanate formed during the reaction, reacts with excess of amine, forming 1,3-disubstituted thiourea.⁷⁷ The thiohydrolysis of cyanamide⁷⁶ and carbodimides suffers from the sluggish nature of the reaction, on account of which secondary changes predominate and the difficulties in obtaining cyanamides, in large yields by amino cyanogen bromide reaction.

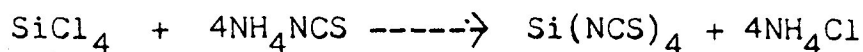
The reaction of isothiocyanate with primary amine gives 1,3-unsymmetrical disubstituted thiourea. This method is advantageous for the synthesis of 1-monosubstituted thioureas, if an unwanted group is removed easily by hydrolysis. The use of benzoyl/carbethoxy isothiocyanate for this reaction was found out.^{78,79} Both these react easily with amine forming the related 1-substituted-3-benzoyl/carbethoxy thiourea which, on alkali hydrolysis gives 1-monosubstituted thiourea. This hydrolysis is readily accomplished in the case of thioureas which are derived from primary amines :-



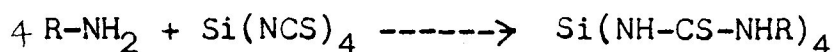
Tertiary butyl isothiocyanate (IX), tertiary amyl isothiocyanate were also used for reaction with aromatic, aliphatic and heterocyclic primary amines to give disubstituted unsymmetrical thioureas (X), which on acid hydrolysis give respective 1-substituted thioureas.⁸⁰



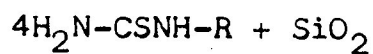
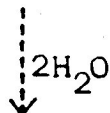
Similar method using silicon tetraisoithiocyanate as thiocarbonylating agent for preparation of substituted thiourea was found out by Neville et al.⁸¹ Silicon tetraisoithiocyanate (XI) was prepared by reaction between ammonium isothiocyanate and silicon tetrachloride (XII) in benzene. This forms complex (XIII) with primary amine which on hydrolysis gives free 1-monosubstituted thioureas.



(XI)



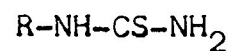
(XIII)



(Thiourea)

Among all these methods for preparation of thiourea, Douglass and Dain's method⁷⁸ (1934) was found to be most convenient. Hence, using this method some 1-mono-substituted thioureas were prepared which are listed in Table - 2.



TABLE-2 : Urea, 1-monosubstituted-2-thio.

No.	R	Mol. formula	Yield %	M.p. °C		REFERENCE
				Found	Reported	
1.	Phenyl	$\text{C}_7\text{H}_8\text{N}_2\text{S}$	38	153	154	82
2.	Benzyl	$\text{C}_8\text{H}_{10}\text{N}_2\text{S}$	32	166	165	79,80
3.	p-Chlorophenyl	$\text{C}_7\text{H}_7\text{ClN}_2\text{S}$	52	173	175	83
4.	p-Bromophenyl	$\text{C}_7\text{H}_7\text{BrN}_2\text{S}$	45	182-183	183	84
5.	p-Fluorophenyl	$\text{C}_7\text{H}_7\text{FN}_2\text{S}$	50	164	164	85
6.	o-Methoxyphenyl	$\text{C}_8\text{H}_{10}\text{N}_2\text{OS}$	57	151	152	83
7.	p-Methoxyphenyl	$\text{C}_8\text{H}_{10}\text{N}_2\text{OS}$	38	167	166	86
8.	o-Ethoxyphenyl	$\text{C}_9\text{H}_{12}\text{N}_2\text{OS}$	45	125-27	127	86
9.	p-Ethoxyphenyl	$\text{C}_9\text{H}_{12}\text{N}_2\text{OS}$	41	170	170-71	87
10.	Phenylethyl	$\text{C}_9\text{H}_{12}\text{N}_2\text{S}$	30	145	147	88
11.	-Phenylethyl	$\text{C}_9\text{H}_{12}\text{N}_2\text{S}$	33	137	138	89
12.	2,4-Dichlorophenyl	$\text{C}_7\text{H}_6\text{Cl}_2\text{N}_2\text{S}$	40	154	154-156	90
13.	3-Methyl-2-pyridyl	$\text{C}_7\text{H}_9\text{N}_3\text{S}$	31	156	157-58	90a
14.	2-Furylmethyl	$\text{C}_6\text{H}_8\text{N}_2\text{OS}$	56	-	-	*

* Available from laboratory.

EXPERIMENTAL

EXPERIMENTALSYNTHESIS OF MONOSUBSTITUTED THIOUREAS :a) 3-Benzoyl-1-(p-chlorophenyl)thiourea :

A mixture of ammonium thiocyanate (16.72 g; 0.22 mole) and freshly distilled acetone (200 ml) was placed in a 500 ml three necked round bottomed flask, equipped with a condenser, a mechanical stirrer and a dropping funnel. It was mounted on steam-bath.

Through a dropping funnel, benzoyl chloride (28.1 g; 0.2 mole) was added with continuous stirring. After the addition was over, the mixture was refluxed for 5 minutes. Then the solution of p-chloroaniline (20.8 g; 0.2 mole) in dry acetone (50 ml) was added, such that the solution refluxed gently. Refluxing was continued further for one hour and then the mixture was poured carefully into 1.0 litre of water. The resulting precipitate of 3-benzoyl-1-(p-chlorophenyl)thiourea was filtered and dried.

Yield : 50.54 g (87.0%); m.p. 139°C.
(Lit.⁷⁸ m.p. 140°C).

b) Hydrolysis of 3-benzoyl-1-(p-chlorophenyl)thiourea :

3-Benzoyl-1-(p-chlorophenyl)thiourea (50.0 g; 0.17 mole) was hydrolysed by boiling with 10% sodium

hydroxide solution in water (150 ml) for 20 minutes. After cooling down, the solution was neutralised with concentrated HCl and was then made slightly basic with aqueous ammonia. The *p*-chlorophenyl thiourea separated out was filtered and dried. It was purified from alcohol.

Yield : 8.8 g (50.2 %); m.p. 173°C.

(Lit.⁸³ m.p. 175°C).

SECTION - A

SYNTHESIS OF 2-(ALKYL/SUBSTITUTED PHENYL/HETERO-
CYCLIC)-4-(N,N-DIETHYL-N'-PHENYL UREA)THIAZOLE

* CHEMISTRY

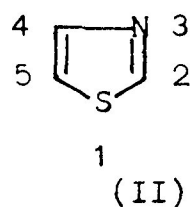
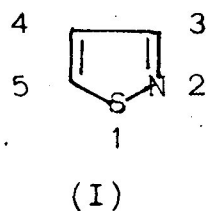
* EXPERIMENTAL

CHEMISTRYSYNTHESIS OF 2-(ALKYL/SUBSTITUTED-PHENYL/HETEROCYCLIC)-
4-(N,N-DIETHYL-N'-PHENYL UREA) THIAZOLE :

The first syntheses of the thiazolic rings were made at the end of the nineteenth century when the initial research was carried out by scientists such as Hantzsch, Hubacher, Traumann, Miolatti, Tcherniac and Gabriel.

Together with the derivatives of pyridine, the thiazoles soon constituted an important part of the heterocyclic chemistry as both, from point of view of the initial research and practical aspect. They are important biologically as well as pharmaceutically, since they appear in the composition of certain vitamins (vitamin B₁) and in penicillins. Reduced thiazoles serve in the study of polypeptides and proteins and occur as structural units in compounds of biological significance.

The thiazole moiety can be exhibited in two different configurations - (I) and (II) as isothiazole and thiazole, respectively.



The isothiazoles (I) have been studied very little and relatively few compounds containing this ring system are known. The thiazoles, on the other hand, have been studied extensively.

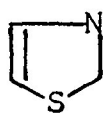
The true thiazole ring (III) possesses two conjugated double bonds. The dihydrothiazoles (IV) possess one conjugated double bond. The dihydrothiazoles (IV) and (V) are designated as thiazolines.



(III)



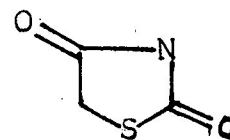
(IV)



(V)



(VI)



(VII)

The 4,5-dihydrothiazole (IV) is commonly referred to as Δ^2 -thiazoline or simply as 2-thiazoline; whereas, 2,3-dihydrothiazole (V) is Δ^4 -thiazoline or 4-thiazoline. Tetrahydrothiazole and unsaturated thiazole ring substituted with oxygen are known as thiazolidine (VI) and thiazolidone (VII) respectively.

Thiazole is structurally related to thiophene as well as to pyridine, but in most of its reactions it resembles the latter. Substituted thiazole similarly resembles the corresponding substituted pyridines rather than the thiophenes. The presence of the annular nitrogen in thiazole ring has two important consequences. Firstly,

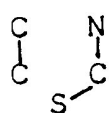
this nitrogen has a lone pair of electrons not involved in bond formation but available for bonding to a proton. Thiazole, therefore, resembles pyridine in being a weak tertiary base. Secondly, the nitrogen produces a general deactivation of the ring to electrophilic substitution and this is further hindered by the fact that such reactions are generally brought about in acid media, so that the thiazole cation is the main species present.

Unless the thiazole is already substituted with an electron donating substituent, nitration, sulfonation or bromination has been found to be relatively difficult.

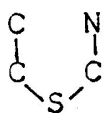
General synthetic methods for thiazole :

Several methods for the synthesis of thiazole compounds are available, which can be classified into partial structures as shown in Scheme - 1.

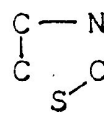




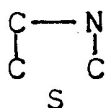
(Ia)



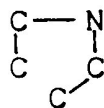
(Ib)



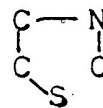
(II)



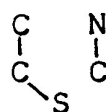
(IIIa)



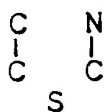
(IIIb)



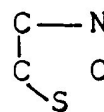
(IIIc)



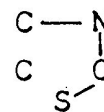
(IVa)



(IVb)



(Va)



(Vb)

SCHEME-1

Various types of ring closures for thiazoles, thiazolines and thiazolidines.

The structure Ia is most useful and versatile of all the thiazole syntheses. By the judicious choice of reactants it allows alkyl, aryl, aralkyl and heterocyclic substituents to be placed in any one of the 2,3,4- or 5-positions of the ring. This method is known by the name of the German scientist Hantzsch who invented it in 1887. It involves the condensation of a compound bearing one halogen and one carbonyl function on two neighbouring carbons. A variety of compounds may serve as nucleophilic

reagents in this reaction such as thioamide, thiourea, ammonium thiocarbamate or dithiocarbamate and derivatives. The two carbon fragments may be α -halocarbonyl compound or their functional derivatives. The importance of this method is clearly reflected by its continued wide use. The method Ib was introduced by Tcherniac who cyclized α -thiacyanatoketones (obtained from α -haloketone and metal thiocyanates) to thiazoles under the action of labile hydrogen compounds. This reaction leads to thiazoles variously substituted in the 2-position depending on the experimental conditions. Although this method has been studied extensively it has limited scope and frequently fails to give thiazoles.

The thiazole ring can be obtained directly by method of Cook and Heilbron using α -aminonitriles or α -aminoamides and carbon disulfide (or thioacid derivatives) as reactant of type II.

The reaction of phosphorus pentasulfide with α -acylamino carbonyl compounds of type IIIa also yields thiazoles. Even more commonly a mercaptoketone is condensed with a nitrile of type IVa or α -mercapto acids or their esters with Schiff bases. This ring closure is limited to the thiazolidines. In the Va ring closure, β -mercapto alkylamines serve as the principal starting material and ethyl formate is the reactant that supplies

the carbon at the 2 position of the ring. These syntheses constitute the most important route for the preparation of many thiazolidines and 2-thiazolines. In the Vb type of synthesis, one of the reactants supplies only the carbon at the 5 position of the resultant thiazole. Then in these latter years new modern synthetic methods of thiazole ring have been developed.

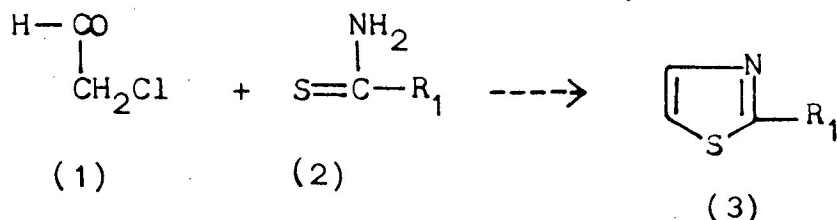
THIAZOLES FROM α -HALOCARBONYL COMPOUNDS :

The cyclization of α -halocarbonyl compounds is carried out with great variety of reactants including thioamides, thioureas, their mono or disubstituted derivatives.

1) Reaction with thioamides :

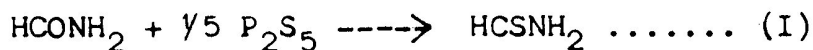
A) Thiazole and its 2-monosubstituted derivatives :

Thiazole (3), $R_1 = H$, can be obtained by condensing chloroacetaldehyde (1) and thioformamide (2), $R_1 = H$.^{91,92}



The reaction is explosive and proceeds in low yield (21%) because of the instability of the thioformamide, that is destroyed as soon as it is cyclized with (1).^{93,94} The thioformamide is prepared in the reaction

mixture by condensing phosphorus pentasulfide and formamide at room temperature, in dioxane solution, according to reaction (I).

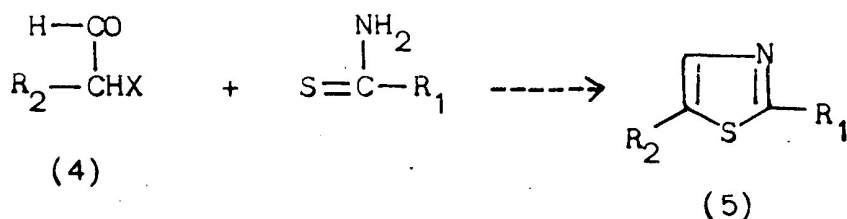


When chloroacetaldehyde is condensed with higher thioamides prepared from amides and phosphorus pentasulfide according to Schwarz's method,⁹⁵ 2-substituted thiazoles are obtained.⁹⁶⁻⁹⁹

Aliphatic thioamides cyclized with α, β -dibromo ether in the presence of MgCO_3 as base, yield the corresponding 2-alkylthiazole in 20 to 60 % range.¹⁰ α -Bromoacetal condensed, with thiobenzamide also give 2-phenylthiazole.

B) 5 and 2,5-disubstituted thiazoles :

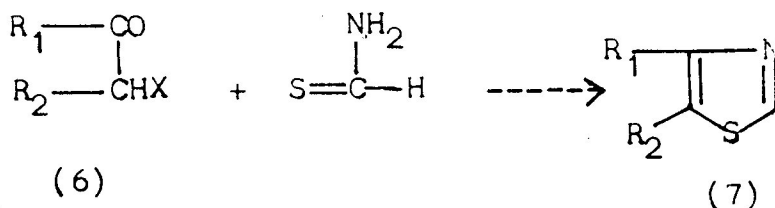
The cyclization of α -haloaldehydes (4) with thioformamide has been reported^{96-98, 101, 102} to give the products 5-alkyl or arylthiazoles (5), $R_1 = \text{H}$, $R_2 = \text{alkyl}$ or aryl.



The reaction of α -bromo (or α -chloro) aldehydes with higher thioamides gives 2,5-dialkyl, diaryl, or arylalkyl thiazoles with yields rarely exceeding 60%. Thioformamide is prepared in situ at 25 to 30°C in the presence of MgCO_3 . The mixture is then mildly heated on water-bath, and when temperature reaches 70°C, α -haloaldehyde is added in small quantities. At the end of this addition the reaction mixture is stirred for 2 hours at 100°C. Thiazoles were then isolated by double steam distillation.

C) 4-Monosubstituted and 4,5-disubstituted thiazoles :

The only method that yields the 2-unsubstituted thiazole derivatives directly, involves the condensation of α -haloketones with thioformamide. The yields obtained are better when bromoketones are used instead of α -chloro-ketones. Cyclization can be achieved by adding ketones dissolved in dioxane in small quantities to the thioformamide formed in situ at below 40°C. The temperature is kept below 70°C during the addition and then reaction mixture is maintained at 100°C, for several hours. Depending on the starting ketone (6), the reaction leads to the formation of 4-monosubstituted or 4,5-disubstituted thiazoles (7) as shown in Scheme-4.



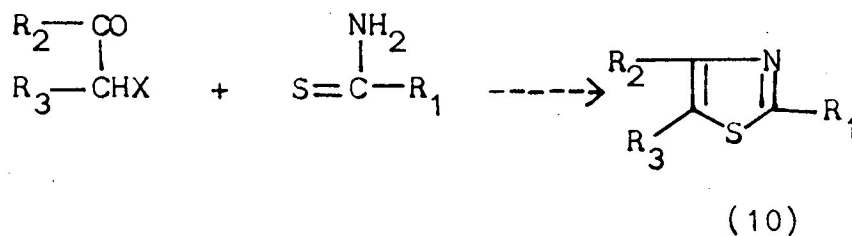
SCHEME - 4

The 4-arylthiazoles are obtained from phenacyl bromide and its substituted derivatives in 40 to 87% yields¹⁰³⁻¹⁰⁵ and 4-phenyl-5-methyl thiazole¹⁰⁶ and 4,5-diphenyl thiazole¹⁰⁷ from α -bromopropiophenone and desyl chloride respectively.

D) 2,4-Disubstituted and 2,4,5-trisubstituted-thiazoles :

The reaction of thioamide with α -halocarbonyl compounds has been applied extensively, and many thiazoles (10) with alkyl, aryl, aralkyl or heteroaryl functional groups at the three 2-, 4- or 5-positions have been reported.

In this section successively each class of these compounds can be examined.

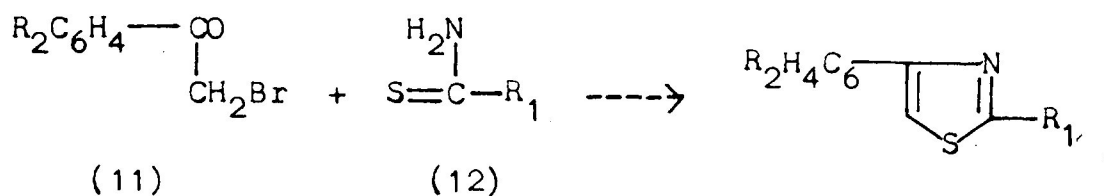


i) 2,4-Dialkyl thiazoles and derivatives :

The condensation of α -haloalkyl ketone (6) $R_3 = H$, with alkyl thioamides or their derivatives gave 2,4-dialkyl thiazoles e.g., 2,4-dimethyl thiazole (10), $R_1 = R_2 = Me$; $R_3 = H$ was prepared for the first time in 1890 by Hubacher¹⁰⁸ and Roublef¹⁰⁹ from chloroacetone and thioacetamide, but the yields were low because of instability of the thioamide in acidic medium.

ii) 2,4-Aralkyl or alkylaryl thiazoles and 2,4,5-trisubstituted thiazoles :

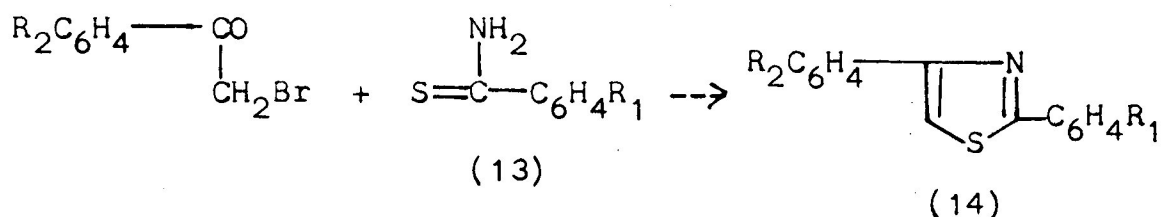
Alkylthioamides and their substituted derivatives have been condensed with ω -bromoacetophenones (11) to give 2-alkyl-4-aryl thiazoles (12) in fairly good yields.^{110,111}



4-Alkyl-2-aryl thiazoles and 4,5-disubstituted-2-(p-aminophenyl) thiazoles were similarly prepared from arylthioamides and α -halomethyl ketones in alcoholic or acetic solution.

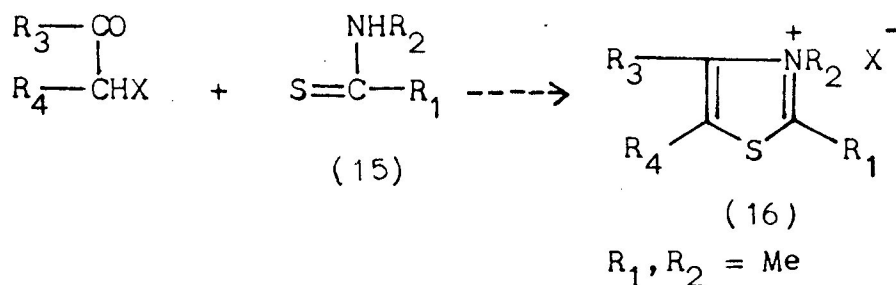
iii) 2,4-Diaryl thiazoles :

2,4-Diaryl thiazoles (14) were prepared in 1950 by Erlenmeyer et al. from thiobenzamide (13) and ω -bromoacetophenones in alcoholic solution, with yields of the order of 50%; whereas, the 2,4-diphenyl thiazole, $R_1 = R_2 = H$ was obtained in 80-85% yield.^{107,108,112}



E) 2,3-Disubstituted and 2,3,4-trisubstituted-thiazoles (Thiazolium salts) :

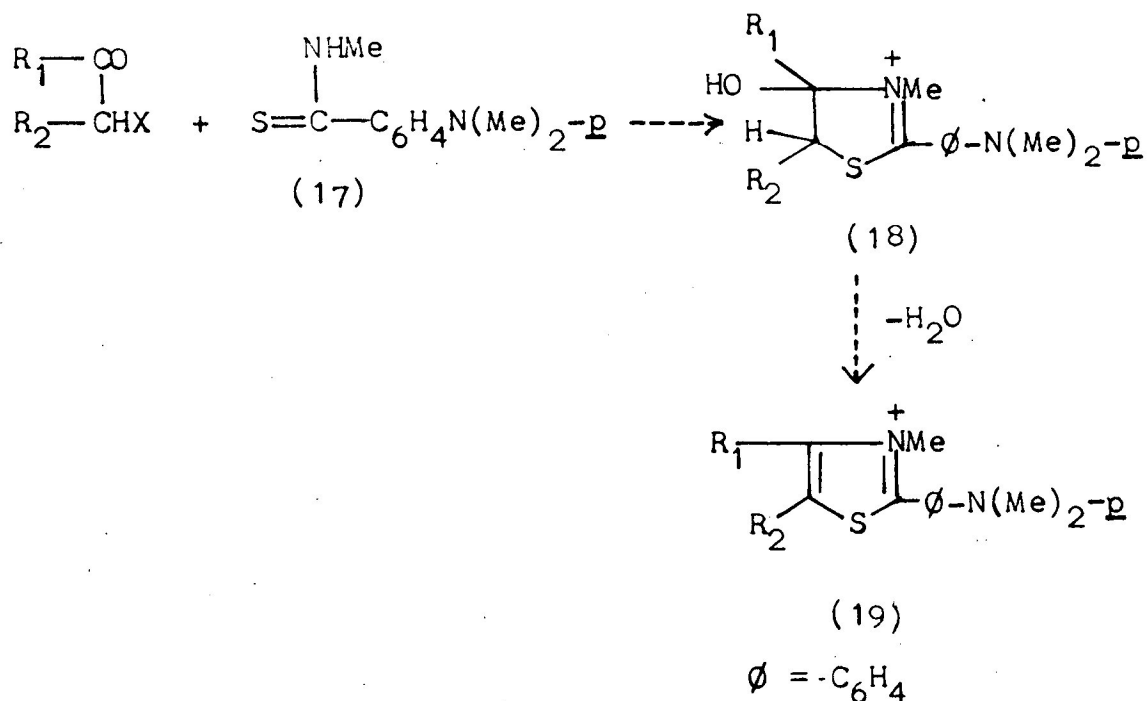
Thiazolium salts can be obtained by a modification of the Hantzsch's thiazole synthesis. This method is valuable for those thiazolium compounds in which the substituent on the ring nitrogen cannot be introduced by direct alkylation, e.g., aryl or heteroaryl thiazolium salts (Scheme-5)¹¹³⁻¹¹⁷



SCHEME - 5

N-Monosubstituted thioamides (15) have been cyclized with α -halocarbonyl compound to give thiazolium salts (16) in excellent yields.

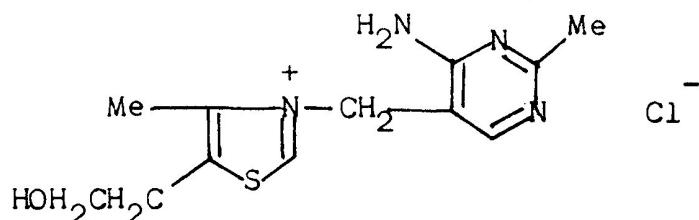
The reaction of N-methyl-(p-dimethyl amino)thio-benzamide (17) with a number of α -haloketones and α -bromo-heptaldehyde gave stable 4-hydroxythiazolinium salts (18) which could be subsequently dehydrated by methanolic hydrogen chloride to the thiazolium salts (19) (Scheme-6).



SCHEME - 6

Thiazolium salts with alkyl,^{117,118} arylalkyl,¹¹⁹ aryl¹¹⁶ or heteroaryl¹¹⁸ substituents on the nitrogen have been also prepared by this procedure. N-substituted thioamides can be formed directly in the reaction mixture

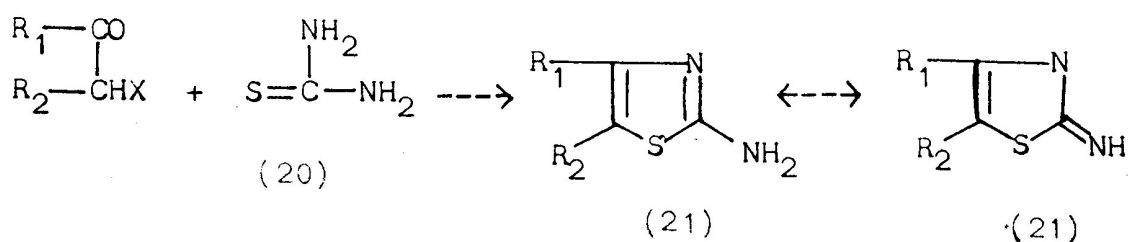
from phosphorous pentasulfide and N-substituted amides.⁹² These methods are important in the synthesis of thiamine (vitamin B₁).



2) Reaction with Thiourea :

A) 2-amino thiazoles :

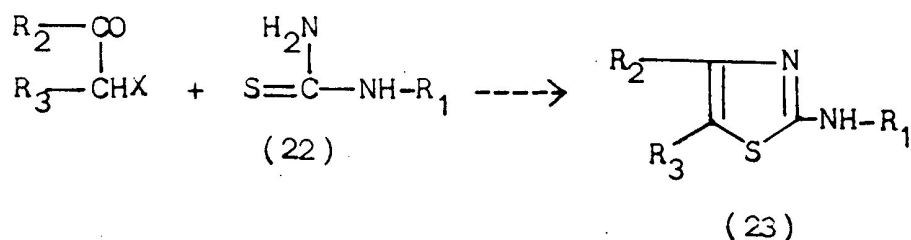
Of all the methods described for synthesis of thiazole compounds, the most efficient involves the condensation of equimolar parts of thiourea (20) and α -haloketones or aldehydes to yield the corresponding 2-amino thiazoles (21).



This method was initially proposed by Popp¹²⁰ and Traumann.¹²¹ The antimicrobial and fungicidal properties of this class of compounds^{122,123} give them great commercial importance.

B) 2-Monosubstituted amino thiazoles :

The cyclization of N-monosubstituted thioureas (22) with halocarbonyl compounds gives 2-monosubstituted-amino thiazoles (23).¹²³



Various 4,5-disubstituted-2-arylamino thiazoles (22) $\text{R}_1 = \text{C}_6\text{H}_4\text{R}$ with $\text{R} = \text{O}$, m- or p-Me, HO_2C , Cl, Br, H_2N , NHAc, NR_2 , OH, OR, O_2N were obtained by condensing the corresponding N-aryl thiourea with chloroacetone,^{124,125,126} dichloroacetone,^{127,128} phenacyl chloride or its p-substituted methyl, t-butyl derivatives, or 2-butanone,¹²⁶ acetophenone or its p-substituted derivatives,^{129,130} ethyl acetate,¹³¹ ethylacetyl propionate,¹³² α,β -unsaturated ketones, benzylidene acetone, furfurylidene acetone or mestyl oxide in the presence of Br_2 or I_2 condensing agent.

MECHANISM OF ACTION FOR THIAZOLE SYNTHESIS

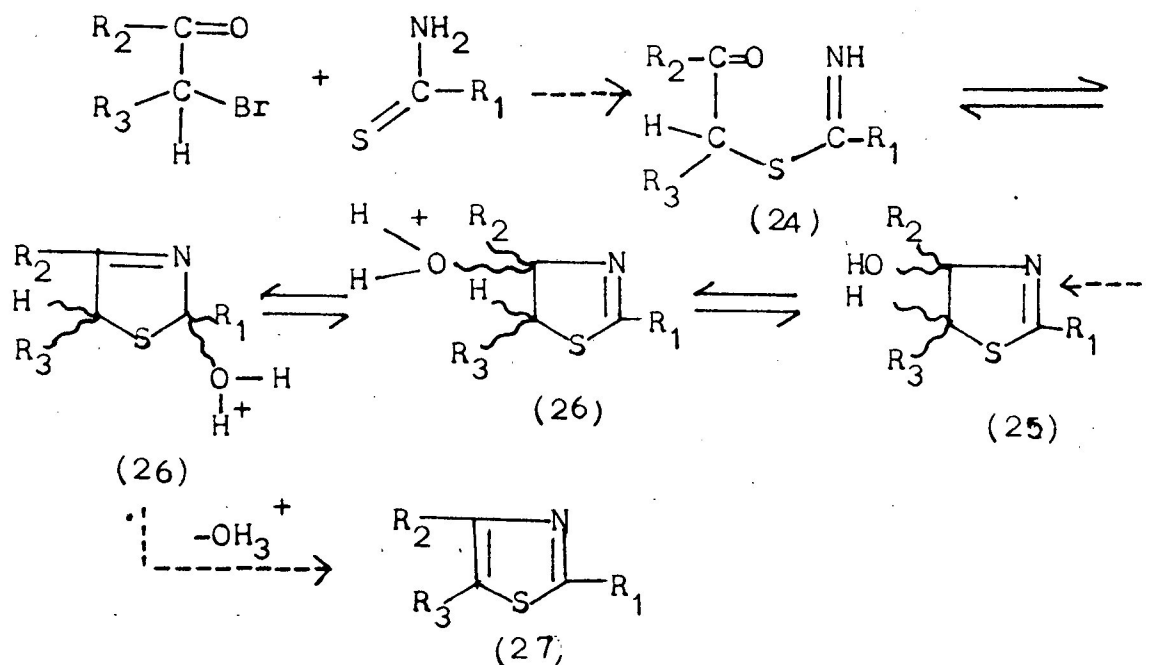
(Hantzsch's Synthesis) :

The mechanism of Hantzsch's synthesis was studied at a very early stage by several authors. The intermediates were generally assumed to be open chain α -thioketones, but in a series of papers by Muraveva and Shchukina^{133,134}

the isolation of hydroxy thiazolines from the reaction between α -haloketones and a variety of thioureas was reported.

The use of reagents bearing a basic centre or the addition of a base to the reaction mixture was recognised as necessary to prevent the acid catalysed elimination of the elements of water from the intermediates. After the publication of this work, a number of similar intermediates have been isolated from thioamides and α -halogeno carbonyl compounds¹³⁵⁻¹³⁹ and as a result of kinetic studies, the exact mechanism of action of this reaction has been well established.

In this type of synthesis, the ring closure can be presented as occurring stepwise, as shown in Scheme-7 below :



SCHEME - 7

The first step in this reaction is the formation of an acyclic intermediates (24) by nucleophilic attack of the sulfur by one of its lone pairs of electrons, on the halogen carrying carbon to form the C-S-C bond.

The next step is attack at the carbon carrying the carbonyl function by the lone pair of nitrogen atoms, giving rise to a new cyclic intermediate (25). This intermediate upon treatment by acid lead to thiazole (27) by loss of H_3O^+ from 26a or 26b.

CHEMISTRY OF p-AMINOPHENACYL CHLORIDE :

p-Amino phenacyl chloride is prepared by Friedel-Craft's reaction.

Friedel Craft's reaction :

In 1877, Charles Friedel and James Crafts reported the action of metallic aluminium on amyl chloride. As a result of this work and their later investigations, including studies of the action of aluminium chloride on amyl chloride and on a mixture of amyl chloride and benzene (to produce amyl benzene), the name Friedel-Crafts has been applied to reactions brought about by the use of anhydrous aluminium chloride or other inorganic halides.

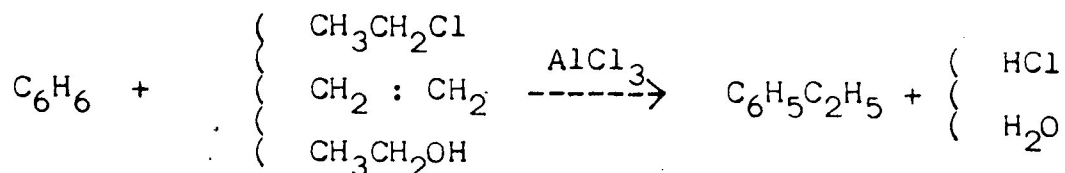
In most restricted sense, Friedel-Crafts reactions

denote only substitution of nuclear hydrogen in aromatic or heteroaromatic compounds to form (1) hydrocarbons and their derivatives or heteroaromatic derivatives (alkylation), (2) ketones or aldehydes (acylation).

In a broader sense, the term includes other reactions catalyzed by aluminium chloride and certain other halides. Other catalysts than anhydrous aluminium chloride that bring about reactions of similar types are anhydrous ferric chloride, hydrogen fluoride, sulfuric acid, boron trifluoride, stannic chloride, phosphoric acid, zinc chloride and antimony pentachloride.

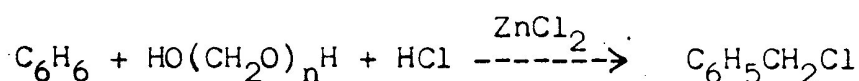
1) Hydrocarbon synthesis (alkylation) :

a) Alkylation of aromatic hydrocarbons and other aromatic and heteroaromatic compounds (e.g., phenols and thiophene) with alkyl halide and certain other aliphatic halogen compounds, olefins, alcohols and ethers.



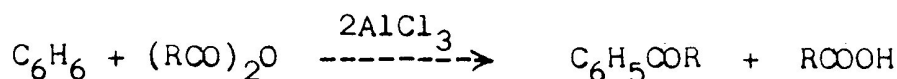
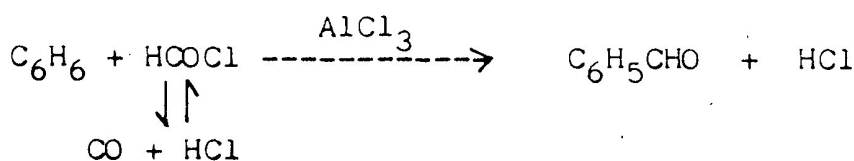
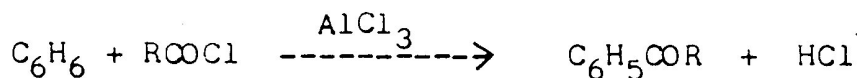
Since in most cases the reaction does not stop with the introduction of one alkyl group, mixtures of products result. Further the reaction is reversible so that transfer of alkyl groups sometimes takes place.

b) Chloromethylation of aromatic compounds : Replacement of a nuclear hydrogen of aromatic hydrocarbon and various derivatives with the chloromethyl group in which paraformaldehyde and hydrochloric acid or chloromethyl ether is used as a source of chloromethyl groups and aluminium chloride, zinc chloride, sulfuric acid or hydrogen chloride is used as catalyst.



2) Synthesis of ketones and aldehydes :

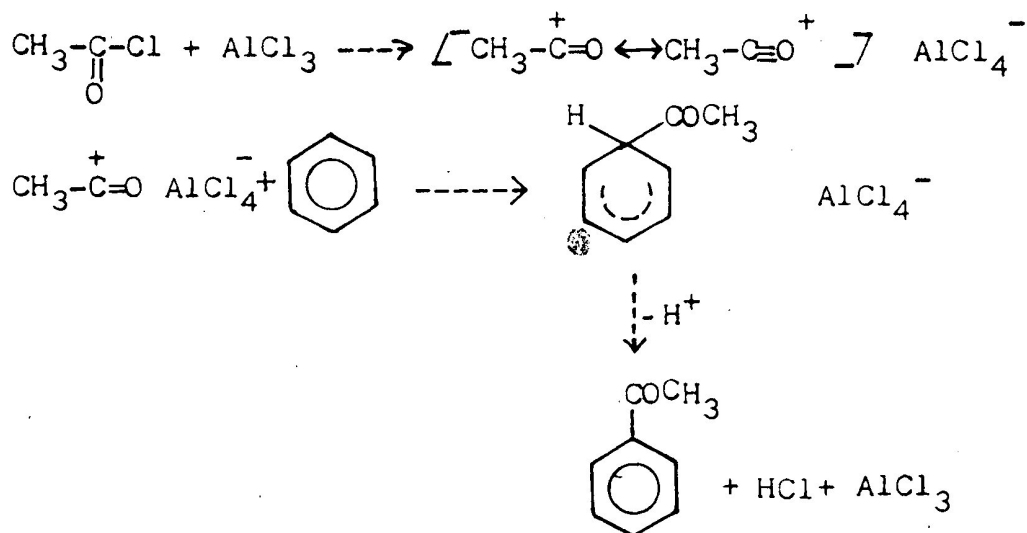
Reactions of aromatic compounds with acyl halides (or carbon monoxide with or without hydrogen chloride), acid anhydrides and esters -



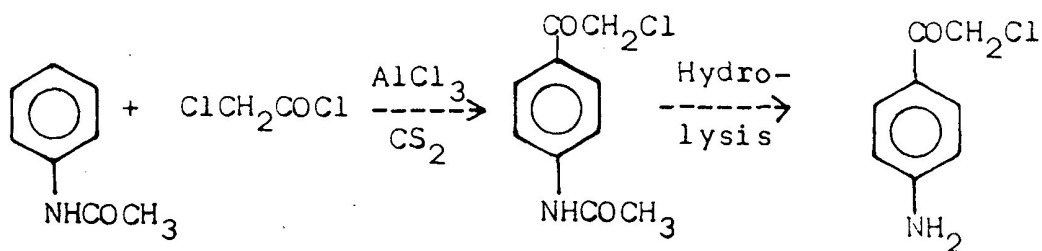
Reactions of this type are generally more satisfactory than the hydrocarbon syntheses because they stop after one acyl group has been introduced and no rearrangement takes place.

Mechanism of reaction :

Acid chlorides or anhydrides in the presence of Lewis acids such as anhydrous AlCl_3 , BF_3 , etc. yield an acylium ion $\text{R}-\overset{+}{\text{C}}=\text{O}$ which acts as an effective electrophile to form ketone.

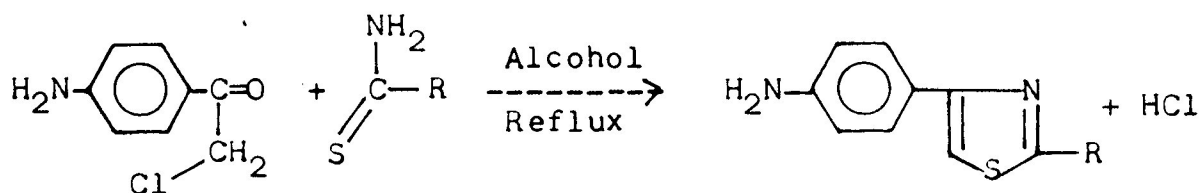


In the present synthetic work, the α -chloro-*p*-amino acetophenone or *p*-amino phenacyl chloride was prepared by using acetanilide as reactant, chloroacetyl chloride as electrophile, and aluminium chloride as a catalyst, in presence of carbon disulfide as a solvent. The reaction can be written as shown in the Scheme :



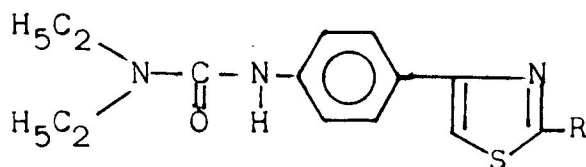
Syntheses of 2-(substituted-phenyl/heterocyclic)-4-(p-aminophenyl) thiazoles :

When substituted phenyl or heterocyclic thioamides and p-aminophenacyl chloride in equimolar quantities refluxed together for 4 to 6 hours in absolute alcohol, the title product was formed. It was filtered and triturated with dilute aqueous ammonia to make it free from HCl which was formed during reaction. Then compound was filtered and washed with water. Solid then obtained was dried and purified from alcohol.



R = Substituted-phenyl, heterocyclic, alkyl.

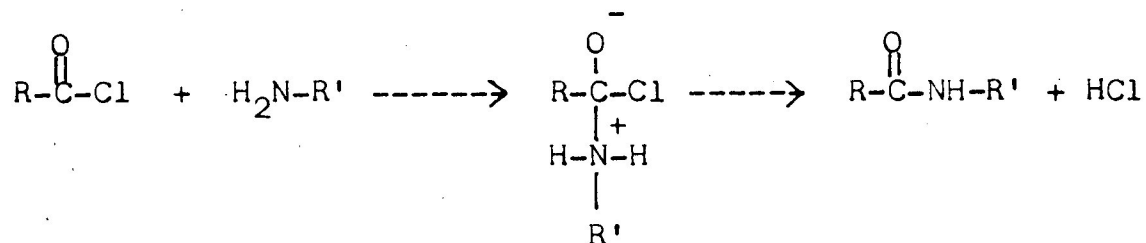
Syntheses of 2-(substituted-phenyl/heterocyclic)-4-(N,N-diethyl-N'-phenyl urea)thiazoles :



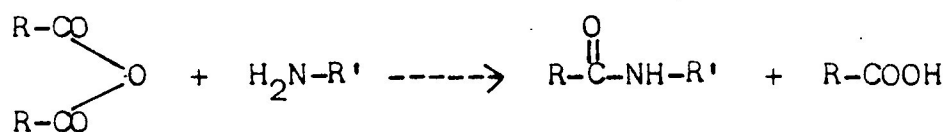
R = Substituted-phenyl, heterocyclic.

Synthesis of the above compound can be looked upon as the preparation of amide compound. Amide linkage can be formed by 4 ways.

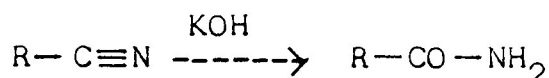
1) By the action of acid chloride on amine.



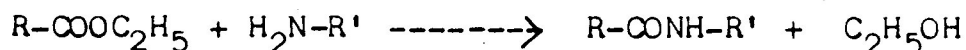
2) By the action of acid anhydride on the amine.



3) By the hydrolysis of nitriles in alkali.



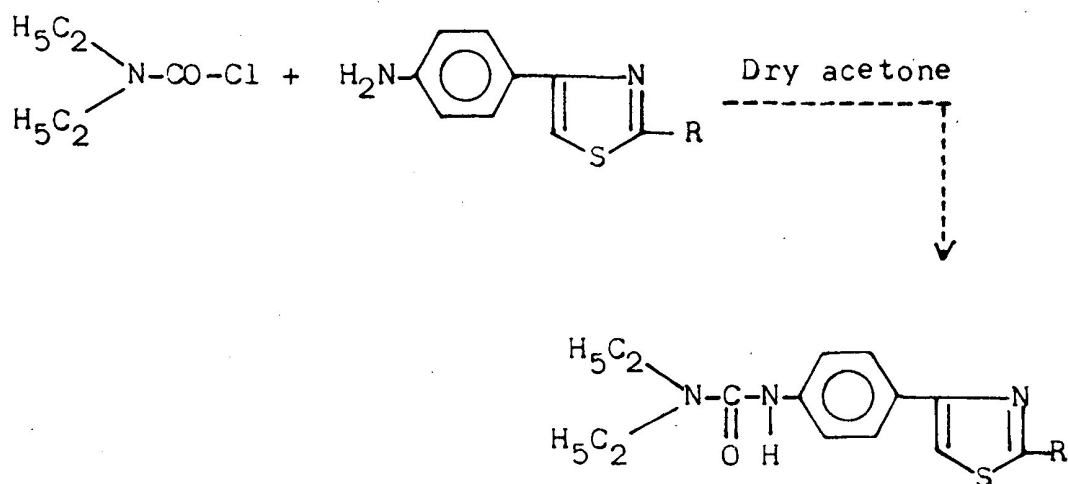
4) By the reaction of acid ester with an amine.



Out of these four methods, first method was found to be suitable for its convenience and easy availability of the carbamoyl chloride required in the synthesis.

The title compounds were prepared by condensing together equimolar quantities of N,N-diethyl carbamoyl chloride and 2-(substituted-phenyl/heterocyclic)-4-(p-amino phenyl) thiazole in dry acetone or dry alcohol at room temperature. It was left overnight, refluxed for

one hour to complete the reaction. The free amino group of the phenyl ring at position 4 of the thiazole reacts with N,N-diethyl carbamoyl chloride to form amide linkage. The final compound was washed with ether and purified from ethyl alcohol.



R = Alkyl, substituted-phenyl, heterocyclic.



EXPERIMENTAL



EXPERIMENTAL

a) p-Chloroacetyl acetanilide :

A mixture of powdered acetanilide (20.0 g; 0.15 mole), chloracetyl chloride (33.54 g; 0.26 mole) and dry carbon disulfide (110 ml) was taken in a one litre, three-necked round bottom flask equipped with mechanical stirrer, double walled condenser and guard tube. This mixture was stirred and while stirring, aluminium chloride (60.0 g; 0.45 mole) was added in 5 to 10 gm portions to it. After addition, the reaction mixture was heated on water-bath, at reflux temperature with vigorous stirring till evolution of hydrochloric gas ceased. Then the mixture was allowed to stand for one hour, when it separated into two layers. The upper CS₂ layer was discarded. The lower reddish brown viscous layer was poured on crushed ice (0.5 kg) to which concentrated hydrochloric acid (40 ml) had been added. The solid compound that separated out was filtered and washed with cold water, till it was free from acid. Thus, p-chloro-acetyl acetanilide obtained was dried in air and was confirmed by its melting point.

Yield : 28.6 g (90.2 %); m.p. 214°C.

(Lit.¹⁴⁰ m.p. 213-214°C).

b) α -Chloro-p-amino acetophenone :

Dilute hydrochloric acid (100 ml, 50%) was added to the p-chloroacetyl acetanilide (25.0 g; 0.12 mole). This mixture was heated with occasional shaking, when clear brown red solution was formed. After refluxing the solution for ten minutes and the cooling down it to room temperature, it was filtered. The filtrate was neutralised with aqueous ammonia in cold condition. The yellow solid separated was filtered and dried. Thus, α -chloro-p-amino acetophenone obtained, was purified from benzene.

Yield : 13.06 g (65.2 %); m.p. 148°C.

(Lit.¹⁴¹ m.p. 146-148°C).

c) 2-(Phenyl)-4-(p-aminophenyl)thiazole :

A mixture of α -chloro-p-amino acetophenone (1.7 g; 0.01 mole) and benzothioamide (1.4 g; 0.01 mole) in dry ethanol (15 ml) was refluxed for four hours. The excess of solvent was removed by evaporation. The solid 2-(phenyl)-4-(p-aminophenyl) thiazole separated in the form of hydrochloric salt was neutralised by aqueous ammonia solution. It was then purified from ethanol.

Yield : 1.51 g (60.4 %); m.p. 144°C.

(Lit.⁵⁰ m.p. 145°C).

d) 2-(Phenyl)-4-(N,N-diethyl-N'-phenyl urea)thiazole :

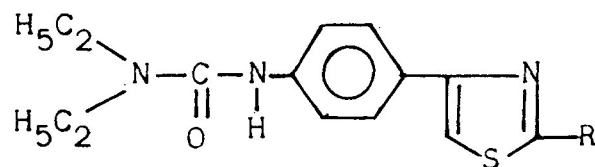
The solution of 2-phenyl-4-(p-amino phenyl)-thiazole (1.0 g; 0.004 mole) in 10 ml of dry acetone was taken in the quickfit conical flask. Triethylamine (0.4 g; 0.004 mole) was added to the reaction mixture and then stirred for half an hour. N,N-diethyl carbamoyl chloride (0.542 g; 0.004 mole) dissolved in dry acetone was added dropwise to the above reaction mixture. Stirring was continued further for 8 hours and then left overnight at room temperature. It was refluxed for one hour to complete the reaction. The solution was then filtered and was heated to evaporate off the excess of solvent. The compound obtained was 2-(phenyl)-4-(N,N-diethyl-N'-phenyl-urea) thiazole. It was washed with ether and then purified from ethanol.

Yield : 0.96 (68.0 %), m.p. 220°C.

Analysis for $C_{20}H_{21}N_3OS$:	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	68.37	5.98	11.96
Found	68.41	5.87	11.73

Similarly, other 2-(alkyl/substituted-phenyl/heterocyclic)-4-(N,N-diethyl-N'-phenyl-urea)thiazole derivatives were prepared. Their physical data is summarised in Table-3.

TABLE-3 : Synthesis of 2-(alkyl/substituted-phenyl/heterocyclic)-4-(N,N-diethyl-N'-phenyl urea) thiazoles.



No.	R	Mol. formula	Mol.wt.	M.p. °C	ELEMENTAL ANALYSIS					
					Reqd. %			Found %		
					C	H	N	C	H	N
1.	Phenyl	$\text{C}_{20}\text{H}_{21}\text{N}_3\text{OS}$	351.1	220	68.37	5.98	11.96	68.41	5.87	11.73
2.	Benzyl	$\text{C}_{21}\text{H}_{23}\text{N}_3\text{OS}$	365	210	69.04	6.30	11.50	69.15	6.12	11.43
3.	p-Methoxyphenyl	$\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$	381	225	66.14	6.03	11.02	65.97	6.23	11.32
4.	3-Methoxy-4-propoxyphenyl	$\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_3\text{S}$	439	79	65.60	6.60	9.56	65.67	6.43	9.23
5.	5-Bromovanillino	$\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}_3\text{SBr}$	476	160-2	52.94	4.62	8.82	52.67	4.60	8.76
6.	2,3-Dichlorophenoxy aceto	$\text{C}_{21}\text{H}_{21}\text{Cl}_2\text{N}_3\text{O}_2\text{S}$	450	215	56.00	4.66	9.33	56.23	4.46	9.56
7.	N,N-Dimethylaminophenyl	$\text{C}_{22}\text{H}_{26}\text{N}_4\text{OS}$	394	295	63.95	6.59	14.39	63.75	6.87	14.46
8.	3-Pyridyl	$\text{C}_{19}\text{H}_{20}\text{N}_4\text{OS}$	352	207	64.77	5.68	15.90	64.59	5.81	15.67
9.	4-Pyridyl	$\text{C}_{19}\text{H}_{20}\text{N}_4\text{OS}$	352	275	64.77	5.68	15.90	64.82	5.42	16.13
10.	Methyl	$\text{C}_{15}\text{H}_{19}\text{N}_3\text{OS}$	289	262	62.28	6.57	14.53	62.52	6.66	14.19

SECTION - B

SYNTHESIS OF 2-(SUBSTITUTED ANILINO/HETEROCYCLIC-
AMINO) -4-(N,N-DIETHYL-N'-PHENYL UREA)THIAZOLE

* CHEMISTRY

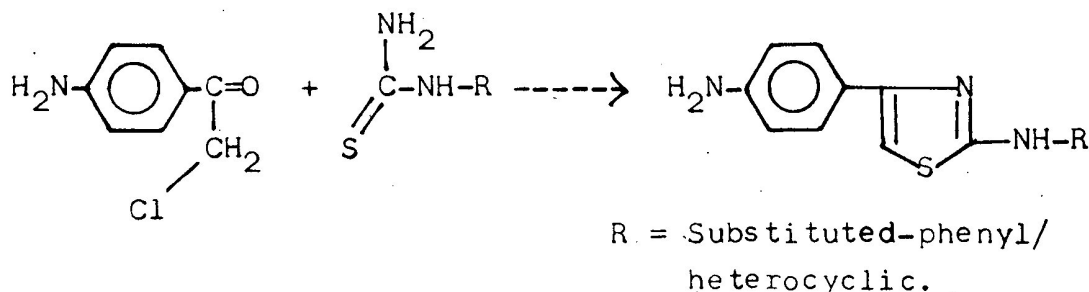
* EXPERIMENTAL

CHEMISTRY

SYNTHESIS OF 2-(SUBSTITUTED ANILINO/HETEROCYCLIC AMINO)-4-(N,N-DIETHYL-N'-PHENYL UREA) THIAZOLES :

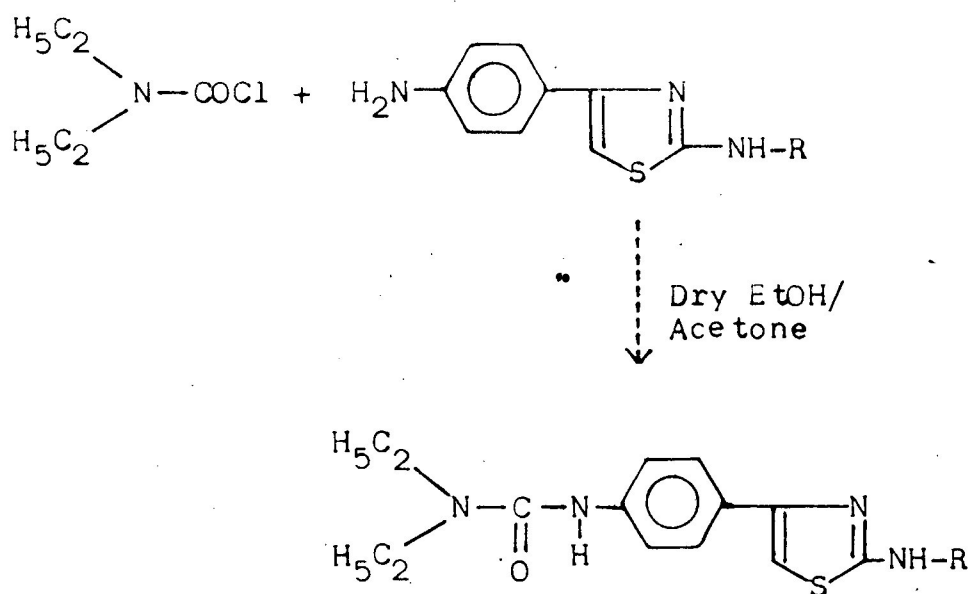
During literature survey it was found that 4-amino phenyl group at position 4 and amino group at 2 position of the thiazole nucleus increases bacteriostatic activity. Therefore, efforts were made to incorporate amino linkage at position 2 of the thiazole along with N,N-diethyl carbamoyl linkage on phenyl ring at position 4 of the thiazole moiety.

The 2-substituted-amino thiazole derivatives were prepared by refluxing together equimolar parts of mono-substituted thiourea and α -haloketone (p-aminophenacyl chloride) in alcohol for 4-6 hours. The final compound 2-(substituted-anilino/heterocyclic amino)-4-(p-amino-thiazole) obtained in the form of hydrochloric salt was freed from acid by triturating with dilute aqueous ammonia.



Thiazole obtained above, was purified from absolute alcohol. Then it was condensed with the N,N-diethyl

carbamoyl chloride using dry acetone or dry alcohol as per the solubility of the thiazole. Solution of N,N-diethyl carbamoyl chloride in dry acetone/alcohol added dropwise with constant stirring to the solution of thiazole in dry alcohol/acetone at room temperature. Stirring continued for 8 hours, then left overnight and refluxed for one hour. Excess of solvent evaporated off. The final title compound obtained was recrystallised from alcohol. Reaction takes place as shown in Scheme-8.



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EXPERIMENTAL

2-(p-Chloroanilino)-4-(p-aminophenyl)thiazole :

A mixture of α -chloro-p-aminoacetophenone (1.7 g; 0.01 mole) and p-chlorophenyl thiourea (1.86 g; 0.01 mole) was dissolved in dry ethanol (15 ml) and was refluxed for four hours. The solid compound 2-(p-chloroanilino)-4-(p-aminophenyl) thiazole separated out in the form of hydrochloric acid was filtered. It was then neutralized by dilute aqueous ammonia solution. The free thiazole was purified from ethanol.

Yield : 2.39 g (79.3%); m.p. 210°C.

(Lit.¹⁴² m.p. 212°C).

2-(p-Chloroanilino)-4-(N,N-diethyl-N'-phenyl urea)-thiazole :

A solution of 2-(p-chloroanilino)-4-(p-aminophenyl)-thiazole (1.0 g; 0.0033 mole) in dry acetone (10 ml) was taken in 100 ml quickfit conical flask, equipped with condenser and guard tube. Triethylamine (0.33 g ; 0.0033 mole) was added to the reaction mixture and then stirred for half an hour. A solution of N,N-diethyl carbamoyl chloride (0.45 g; 0.0033 mole) in dry acetone (10 ml) was added dropwise to the above reaction mixture and was stirred for eight hours. It was then left overnight at room temperature and then refluxed for one hour.

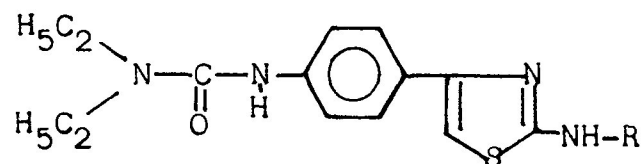
The solution was filtered and excess of solvent was removed by evaporation. The compound 2-(p-chloroanilino)-4-(N,N-diethyl-N'-phenyl urea) thiazole, separated out was filtered and washed with the ether. It was purified from alcohol.

Analysis for $C_{20}H_{21}ClN_4OS$	:	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.		67.00	6.59	14.21
Found		66.87	6.72	14.42

Similarly, other thiazole derivatives of series 2-(substituted anilino)-4-(N,N-diethyl-N'-phenyl urea)-thiazole were prepared and their physical data are described in Table - 4.



TABLE-4 : 2-(Substituted-anilino)/heterocyclic-amino)-4-(N,N-diethyl-N-phenyl urea)-thiazoles.



No.	R	Mol. formula	Mol.wt.	M.p. °C	ELEMENTAL ANALYSIS					
					Reqd. %			Found %		
					C	H	N	C	H	N
1.	Phenyl	C ₂₀ H ₂₂ N ₄ OS	366	120	66.31	6.31	14.73	66.45	6.27	14.91
2.	p-Chlorophenyl	C ₂₀ H ₂₁ ClN ₄ OS	400.5	120	67.00	6.59	14.21	66.87	6.72	14.42
3.	p-Bromophenyl	C ₂₀ H ₂₁ BrN ₄ OS	445	240	53.93	4.71	12.58	54.23	4.83	12.35
4.	p-Fluorophenyl	C ₂₀ H ₂₁ FN ₄ OS	384	210	62.50	5.46	14.58	62.37	5.49	14.89
5.	2,4-Dichlorophenyl	C ₂₀ H ₂₀ Cl ₂ N ₄ OS	345	125	55.10	4.59	12.85	55.32	4.72	12.92
6.	Benzyl	C ₂₁ H ₂₄ N ₄ OS	380	205	66.31	6.31	14.73	66.57	6.29	14.67
7.	1-Phenylethyl	C ₂₂ H ₂₆ N ₄ OS	394	170	67.00	6.59	14.21	66.83	6.47	14.45
8.	2-Phenylethyl	C ₂₂ H ₂₆ N ₄ OS	394	212	67.00	6.59	14.21	66.73	6.31	14.51
9.	o-Methoxyphenyl	C ₂₁ H ₂₄ N ₄ O ₂ S	396	150	63.63	6.06	14.14	63.23	5.91	14.32
10.	p-Methoxyphenyl	C ₂₁ H ₂₄ N ₄ O ₂ S	396	200	63.63	6.06	14.14	63.36	6.12	14.01
11.	o-Ethoxyphenyl	C ₂₂ H ₂₆ N ₄ O ₂ S	410	125	64.38	6.34	13.65	64.05	6.54	13.61
12.	p-Ethoxyphenyl	C ₂₂ H ₂₆ N ₄ O ₂ S	410	205	64.39	6.34	13.65	64.52	6.61	13.37
13.	3-Methyl-2-pyridyl	C ₂₀ H ₂₃ N ₅ OS	381	215	62.29	6.03	18.37	61.90	6.39	18.51
14.	2-Furylmethyl	C ₁₉ H ₂₂ N ₄ O ₂ S	370	125	61.62	5.90	15.13	62.00	5.63	15.21

SECTION - C

SYNTHESIS OF 2-(SUBSTITUTED ANILINO/HETEROCYCLIC
AMINO-4-(N,N-DIETHYL-N'-PHENYL UREA) -5-METHYL
THIAZOLES

* CHEMISTRY

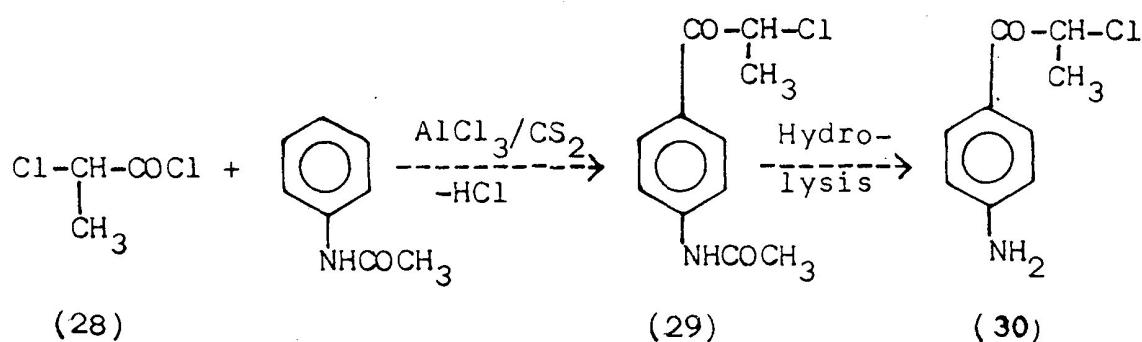
* EXPERIMENTAL



CHEMISTRY

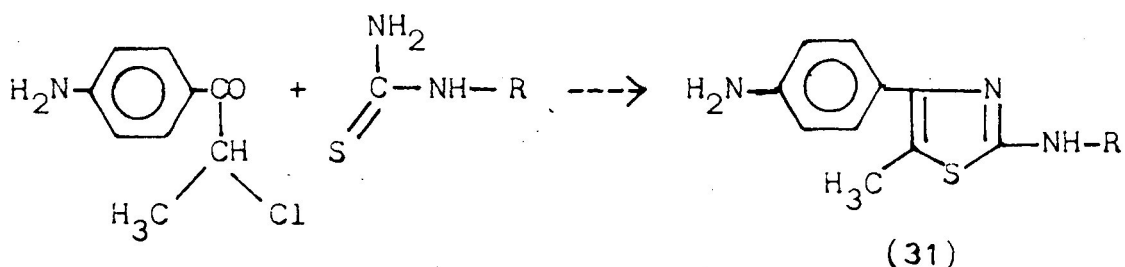
SYNTHESIS OF 2-(SUBSTITUTED ANILINO/HETEROCYCLIC AMINO)-4-(N,N-DIETHYL-N'-PHENYL UREA)-5-METHYL-THIAZOLES :

In this series of thiazole, methyl group was incorporated at the fifth position of ring along with amino linkage at 2 position and changes occurred in its anti-tubercular activity were observed. To incorporate methyl group in the ring, α -chloro-p-amino propiophenone was used as reactant instead of α -chloro-p-amino acetophenone. It was prepared by using Friedel-Crafts' reaction. Reaction between acetanilide, 2-chloropropionyl chloride (28) using dry aluminium chloride as a catalyst and carbon disulfide as solvent under dry conditions gave α -chloro-p-acetyl amino propiophenone (29), which on acid hydrolysis gave free α -chloro-p-amino propiophenone (30). This reaction can be given as shown below :

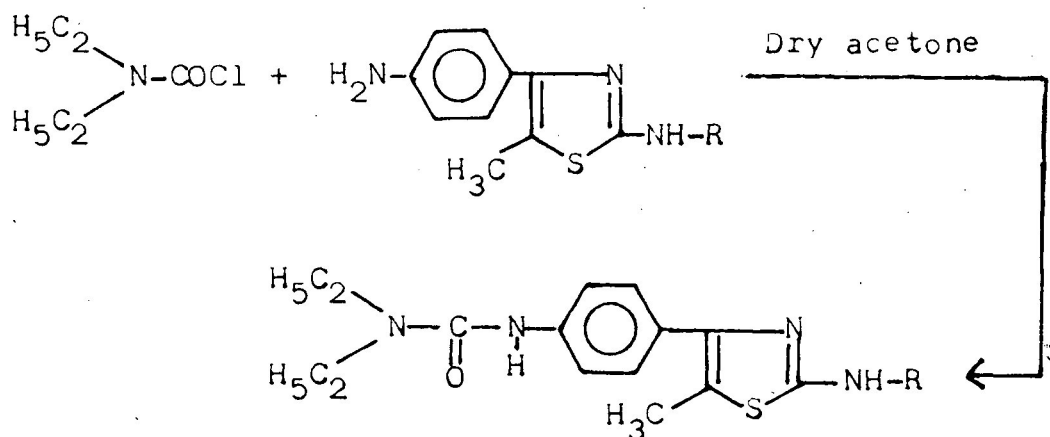


Various monosubstituted thioureas, when refluxed with α -chloro-p-amino propiophenone in alcohol in equimolar

proportion gave corresponding 2-(substituted anilino/heterocyclic amino)-4-(p-aminophenyl)-5-methyl thiazoles (31).



Compound (31) was made free of hydrochloric acid liberated during reaction by triturating it with aqueous ammonia. Compound (31) was dissolved in acetone and to it dropwise with constant stirring, at room temperature, was added solution of equimolar quantity of N,N-diethyl carbamoyl chloride. After 8 hours stirring, reaction mixture left overnight and refluxed for one hour. When excess of solvent was removed, final compound, 2-(substituted anilino/heterocyclic amino)-4-(N,N-diethyl-N'-phenyl urea)-5-methyl thiazole was obtained.



EXPERIMENTAL

EXPERIMENTAL

a) 2-Chloro-p-acetamidopropiophenone :

The mixture of powdered acetanilide (27.0 g; 0.2 mole), anhydrous aluminium chloride (80.0 g; 0.6 mole) and carbon disulfide (200 ml) was taken in 500 ml three-necked round bottom flask equipped with double wall condenser, mechanical stirrer and a dropping funnel. The mixture was stirred well to give uniform suspension. 2-Chloropropionyl chloride (16.0 g; 0.36 mole) was added dropwise to above reaction mixture and temperature was maintained such that gentle refluxing continued. After addition was over, the reaction mixture was refluxed for one hour, and then allowed to stand at room temperature. Reaction mixture separated into two layers. The upper layer of carbon disulfide was discarded, and the lower reddish-brown sticky layer was poured on crushed ice (1/2 kg) to which 20 ml concentrated HCl had been added. The solid compound obtained was filtered, washed with cold water till free from acid and then dried.

Yield : 39.3 g (80.0%); m.p. 118-119°C.

(Lit.⁵⁰ m.p. 117-119°C).

b) 2-Chloro-p-aminopropiophenone :

A mixture of 2-chloro-p-acetamido propiophenone (25.0 g; 0.11 mole) and hydrochloric acid (100 ml, 50%) was

taken in 500 ml round bottomed flask and heated with occasional shaking when clear solution was formed. The solution was refluxed for ten minutes and then poured on cold water. It was neutralised with aqueous ammonia in cold condition. The compound separated out, was filtered, washed with water and then dried. The α -chloro-p-amino-propioophenone thus obtained was confirmed by melting point.

Yield : 12.71 g (63.0%); m.p. 97°C.

(Lit.⁵⁰ m.p. 98°C).

c) 2-(p-Bromoanilino)-4-(p-aminophenyl)-5-methyl thiazole :

α -Chloro-p-amino propioophenone (1.83 g; 0.01 mole) and p-bromophenyl thiourea (2.3 g; 0.01 mole) were dissolved in dry ethanol (20 ml) and refluxed for 4 to 6 hours. The hydrochloric salt of 2-(p-bromoanilino)-4-(p-aminophenyl)-5-methyl thiazole separated out, was filtered and then neutralized with aqueous ammonia. The free thiazole so obtained, was purified from ethanol.

Yield : 2.34 g (65.0%); m.p. 178°C.

Analysis for $C_{16}H_{14}BrN_3S$:	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	53.33	3.88	11.66
Found	53.56	4.03	11.85

d) 2-(p-Bromoanilino)-4-(N,N-diethyl-N'-phenyl-urea)-5-methyl thiazole :

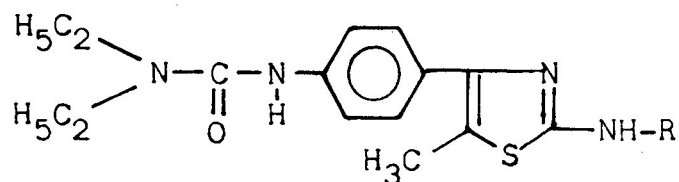
A solution of 2-(p-bromoanilino)-4-(p-aminophenyl)-5-methyl thiazole (1.08 g; 0.003 mole) in dry acetone (10 ml) was taken in 100 ml quickfit conical flask equipped with condenser, and guard tube. Triethylamine (0.3 g; 0.003 mole) was added to it and stirred for half an hour. Then the solution of N,N-diethyl carbamoyl chloride (0.41 g; 0.003 mole) in dry acetone was added dropwise to the above reaction mixture. Stirring was continued further for 8 hours and then left overnight at room temperature. It was refluxed for one hour to complete the reaction. The solution was filtered and heated to evaporate the excess of solvent. The final product obtained was 2-(p-bromoanilino)-4-(N,N-diethyl-N'-phenyl urea)-5-methyl thiazole.

Yield : 0.91 g (65.0 %); m.p. 205°C.

Analysis for $C_{21}H_{23}BrN_4OS$:	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	54.78	5.00	12.17
Found	54.61	5.29	12.01

Similarly, other compounds of the series 2-(substituted anilino/heterocyclic amino)-4-(N,N-diethyl-N'-phenyl urea)-5-methyl thiazoles were prepared. The physical data of these compounds is as shown in Table-5.

TABLE-5 : 2-(Substituted-anilino/heterocyclic amino)-4-(N,N-diethyl-N'-phenyl urea)-5-methyl thiazoles.



No.	R	Mol. formula	Mol.Wt.	m.p. °C	ELEMENTAL ANALYSIS					
					Reqd. %			Found %		
					C	H	N	C	H	N
1.	Phenyl	C ₂₁ H ₂₄ N ₄ OS	380	220	66.31	6.31	14.73	66.37	6.27	14.56
2.	p-Chlorophenyl	C ₂₁ H ₂₃ ClN ₄ OS	414.5	210	60.64	5.53	13.47	60.32	5.61	13.71
3.	p-Bromophenyl	C ₂₁ H ₂₃ BrN ₄ OS	460	205	54.78	5.00	12.17	54.61	5.29	12.01
4.	p-Fluorophenyl	C ₂₁ H ₂₃ FN ₄ OS	398	180	63.31	5.77	14.07	63.57	5.91	13.83
5.	2,4-Dichlorophenyl	C ₂₁ H ₂₂ Cl ₂ N ₄ OS	449	205	56.12	4.89	12.47	56.07	4.67	12.31
6.	3,4-Dichlorophenyl	C ₂₁ H ₂₂ Cl ₂ N ₄ OS	449	165	56.12	4.80	12.47	56.39	5.07	12.53
7.	Benzyl	C ₂₂ H ₂₆ N ₄ OS	394	190	67.00	6.59	14.21	66.85	6.34	14.43
8.	Phenylethyl	C ₂₃ H ₂₈ N ₄ OS	408	130	67.64	6.86	13.72	67.79	6.48	13.61
9.	o-Methoxyphenyl	C ₂₂ H ₂₆ N ₄ O ₂ S	410	200	64.39	6.34	13.65	64.24	6.17	13.49
10.	p-Methoxyphenyl	C ₂₂ H ₂₆ N ₄ O ₂ S	410	185	64.39	6.34	13.65	64.67	6.21	13.82
11.	o-Ethoxyphenyl	C ₂₃ H ₂₈ N ₄ O ₂ S	424	165	65.09	6.60	13.20	65.24	6.26	13.14
12.	p-Ethoxyphenyl	C ₂₃ H ₂₈ N ₄ O ₂ S	424	210	65.09	6.60	13.20	65.31	6.42	13.01
13.	3-Methyl-2-pyridyl	C ₂₁ H ₂₅ N ₅ OS	395	140	63.79	6.32	17.72	63.64	6.02	17.61
14.	2-Furylmethyl	C ₂₀ H ₂₄ N ₄ OS	384	140	62.50	6.25	14.58	62.41	6.36	14.72

SECTION - D

p-(BUTYL)-p¹/4-(2,5-DISUBSTITUTED) THIAZOLYL_7-
THIOCARBANILIDES :

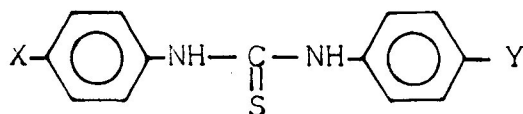
* CHEMISTRY

* EXPERIMENTAL

CHEMISTRY

p-(BUTYL)-p-[4-(2,5-DISUBSTITUTED) THIAZOLYL]-7-THIOCARBANILIDES :

Thiourea and its derivatives are tuberculostatic. Thiourea itself possesses a slight but definite in vitro activity which is enhanced by appropriate substitution, as in allylthiourea.¹⁴³ After the discovery of antimycobacterial activity of thioureas¹⁴⁴ numerous publications have appeared showing the pronounced activity of thiocarbanilides both in vitro as well as in experimental animals coupled with only a low rate of development of resistance.¹⁴⁵ Among the most potent compounds of this class are thiocarbanilides bearing alkoxy groups in para-positions. Some of these viz., 4,4'-diisoamyloxy thiocarbanilides¹⁴⁶ (I); 4,4'-diethoxy thiocarbanilides¹⁴⁷ (II) and 4-butoxy-4'-dimethyl amino thiocarbanilide¹⁴⁸ (III) have been used clinically for the treatment of tuberculosis and leprosy.



- I : X = Y = Isoamyloxy;
 II : X = Y = Ethoxy;
 III : X = Butoxy and Y = N(CH₃)₂ ;
 IV : X = 2-Pyridyl and Y = Isobutoxy.

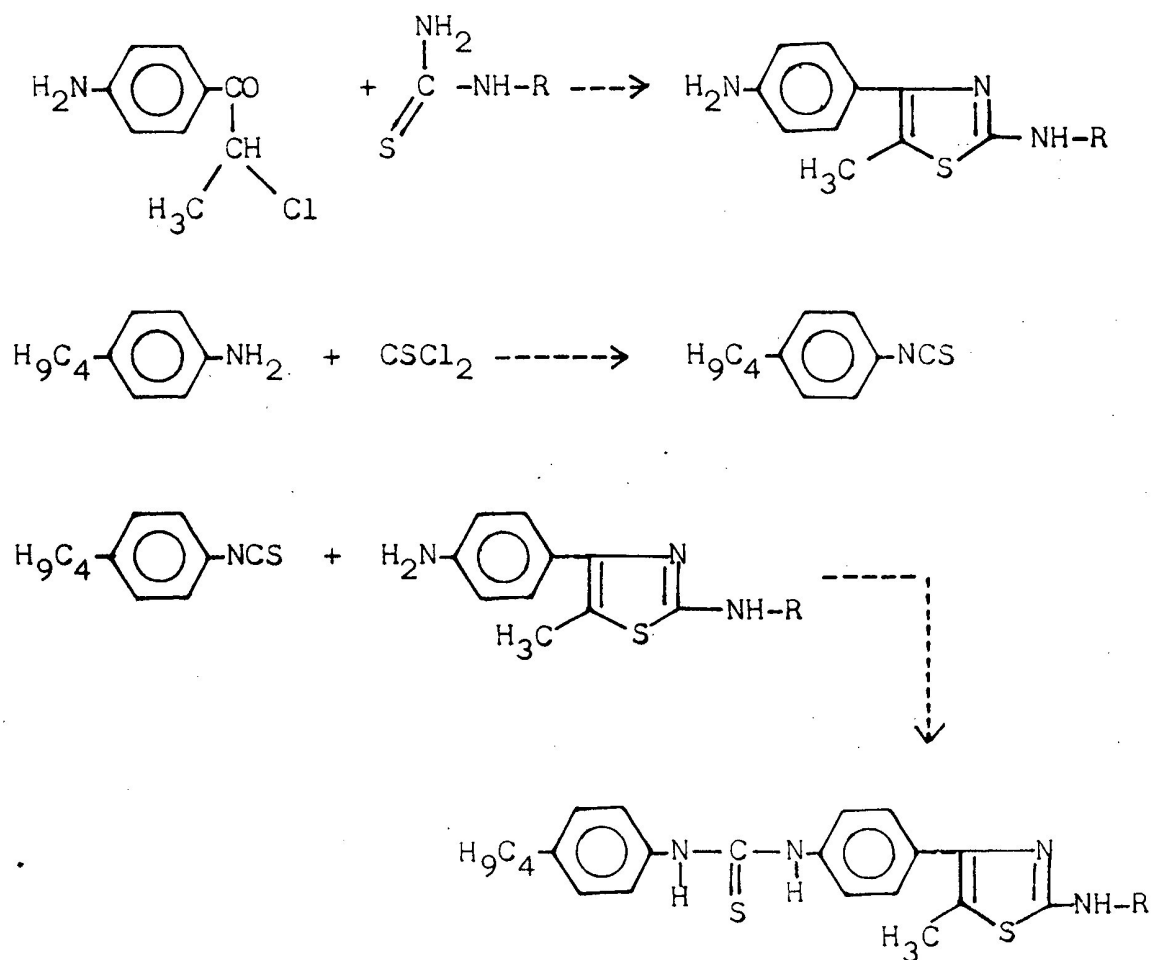
Doub et al.¹⁴⁹ have extended the series of alkoxy thiocarbanilides by incorporating a heterocyclic ring viz., pyridyl as the substituent and observed potentiation of antimycobacterial activity. One of the compounds from their series called thiocarbanilide (IV) showed high degree of antitubercular action in mice and guinea pigs.¹⁵⁰ However, in clinical trials it was not effective, due to poor absorption.¹⁵¹

Since thiazole and pyridine are isosteric and several thiazole derivatives are potent antibacterial agent, various thiocarbanilides having thiazole as substituent were prepared by Kulkarni et al.⁵⁰ Among various p-(2-thiazolyl), p-(4-thiazolyl) and p-(5-thiazolyl)-p-(alkoxy thiocarbanilides), the most active compounds were p-(4-thiazolyl)-p'-alkoxy thiocarbanilides.

Taking lead from this, p-[4-(2,5-disubstituted)-thiazolyl]-p'-butyl thiocarbanilides were prepared. The synthesis of these compounds in present work was effected by the interaction of various 2-(substituted anilino/-heterocyclic amino)-4-(p-aminophenyl)-5-methyl thiazole with equimolar quantity of p-butyl phenyl isothiocyanate in boiling benzene or alcohol.

In the present work, p-butylphenyl isothiocyanate was prepared by reaction between p-butyl aniline and

thiopohosgene. 2-(Substituted anilino/heterocyclic-amino)-4-(p-aminophenyl)-5-methyl thiazole was prepared by reaction between α -chloro-p-amino propiophenone and various substituted thioureas. Final condensation of thiazole and isothiocyanate to get thiocarbanilide is as shown in the Scheme-8.



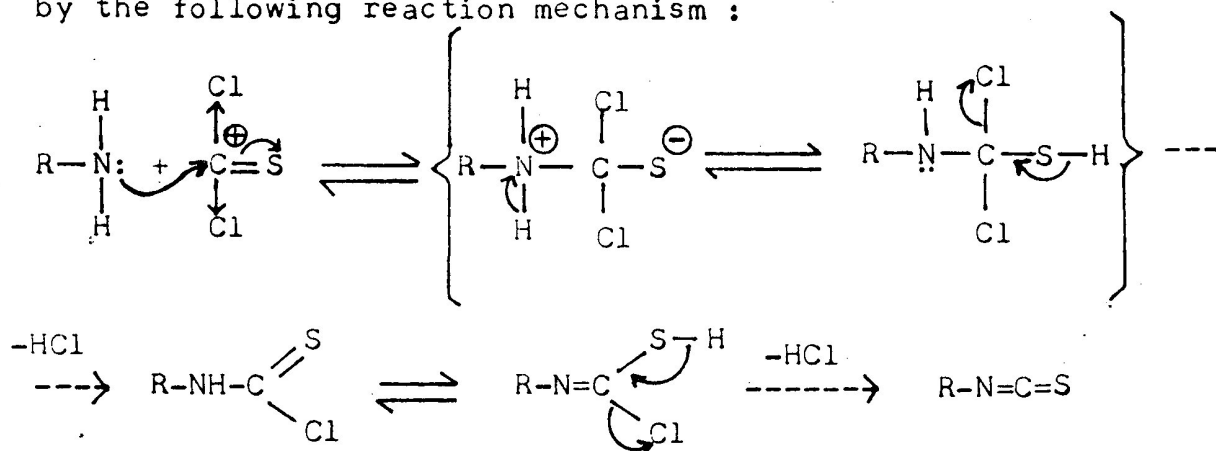
SCHEME - 8

PREPARATION OF ISOTHIOCYANATES :

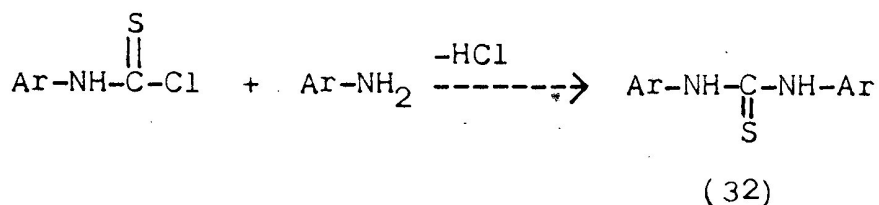
Reactions of amines with sulphur compounds :

a) Thiophosgene :

This method is based on the direct treatment of primary amines with thiophosgene.¹⁵² The first product of the reaction is an unstable thiocarbamoyl chloride which splits off hydrogen chloride easily yielding isothiocyanates.¹⁵³ The course of reaction can be illustrated by the following reaction mechanism :



In case of aromatic amines, especially with electron accepting substituents, N,N'-disubstituted thioureas (32) may be formed as by-product.¹⁵³



The formation of thioureas can be prevented by the use of a small excess of thiophosgene. Since isothiocyanates as well as thiophosgene are relatively insensitive to water they can also be prepared in an aqueous medium.¹⁵⁴

Not only free amines but also their salts, particularly hydrochlorides react with thiophosgene to produce isothiocyanates.¹⁵⁵

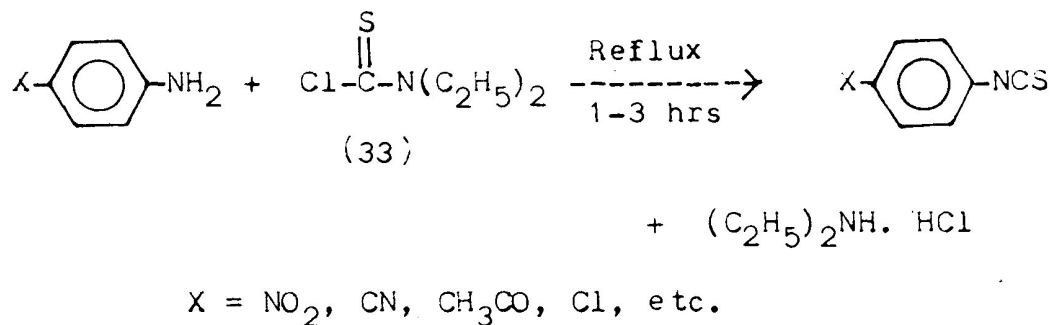
Generally, a solution of arylamine in neutral organic solvent e.g., chloroform,¹⁵⁶ dichloroethane¹⁵⁷ or toluene¹⁵⁸ is added to the water emulsion of thiophosgene. The rate of reaction is retarded by the hydrochloric acid released in the course of reaction. For this reason bases are frequently added to the reaction mixture to bind HCl e.g., CaCO_3 ¹⁵⁷, Na_2CO_3 and NaHCO_3 ^{159,160} or triethylamine.¹⁶¹

Arylamines which are highly susceptible to atmospheric oxidations may be used in the form of hydrochloric salt.

b) Thiocarbamoyl derivatives :

N,N-Diethyl thiocarbamoyl chloride is a new reagent which could replace the use of toxic thiophosgene reagent.¹⁶² It is one step method and consists of heating arylamine with N,N-diethyl thiocarbamoyl chloride (33) in

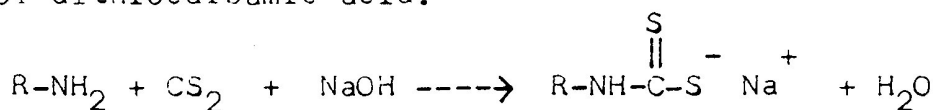
an inert solvent such as chlorobenzene, benzene, toluene or ethylene dichloride. With increase in the basicity of amine, the yields of isothiocyanates decrease.



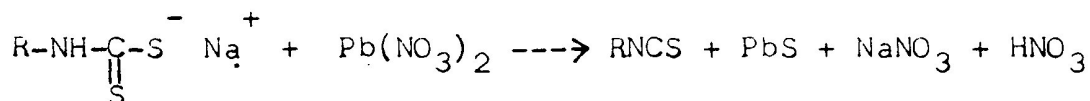
DECOMPOSITION OF DITHIOCARBAMIC ACID AND ITS SALTS OR ESTERS :

a) Decomposition by heavy metal salts :

Synthesis of isothiocyanate takes place in two steps. In first step action of carbon disulfide and alkali^{163,164} or ammonia¹⁶⁵ on the aqueous or organic (alcohol, methylene chloride, toluene, etc) solution of primary amine gives salt of dithiocarbamic acid.



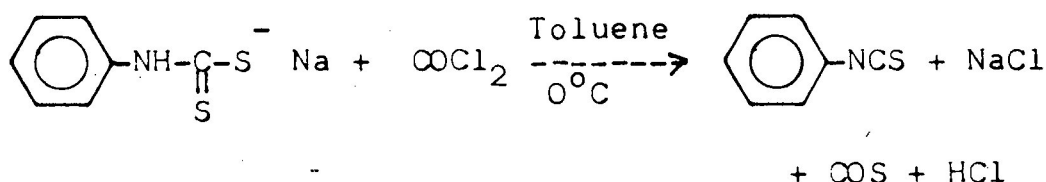
In second step heating of alkaline dithiocarbamate with heavy metal salts gives corresponding isothiocyanate and metal sulfide.¹⁶⁶



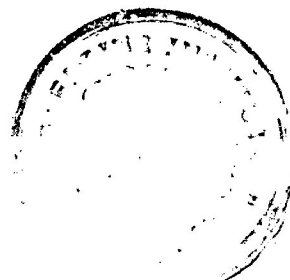
Heavy metal salts such as mercury salts,^{166,167} lead nitrate,^{169,170} cupric sulphate,¹⁶⁷ ferric chloride,¹⁷¹ are used.

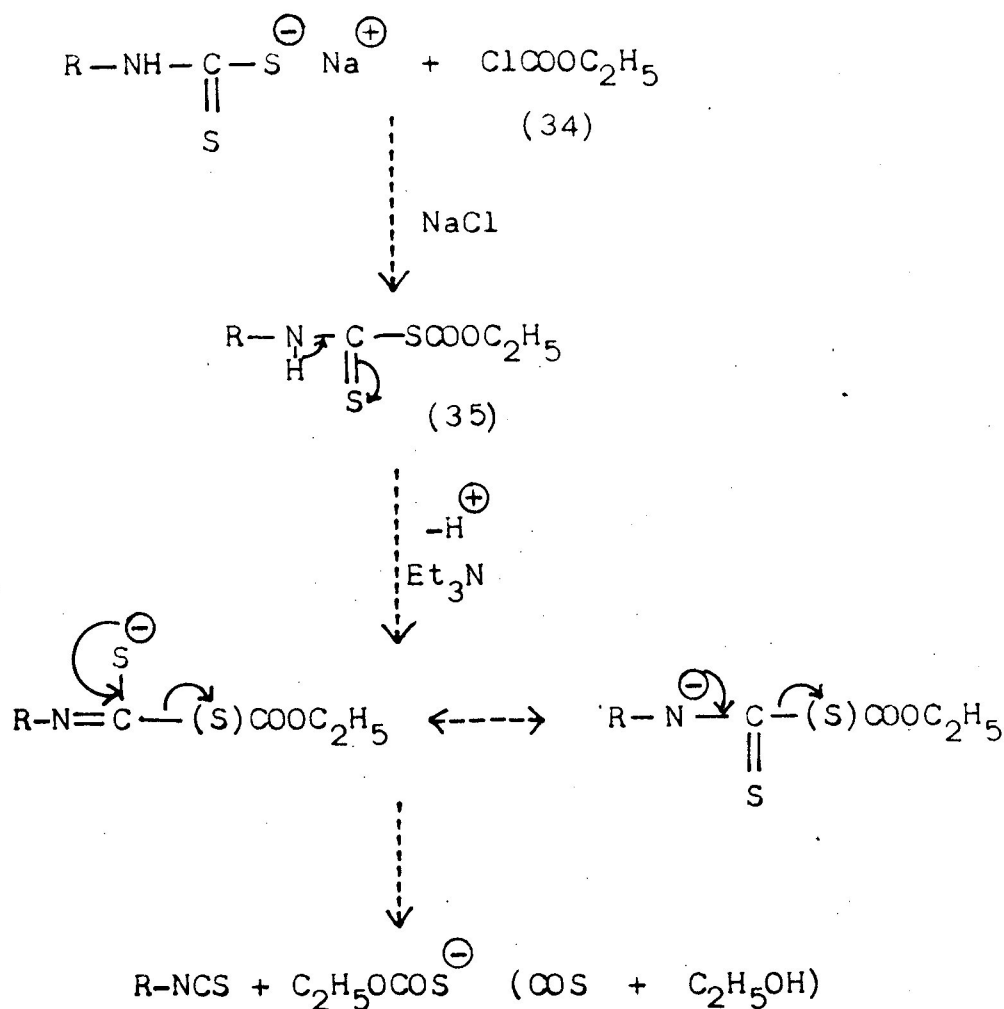
b) Decomposition by chlorine containing compounds :

Some aromatic isothiocyanates are prepared by decomposition of dithiocarbamates with phosgene.¹⁷²

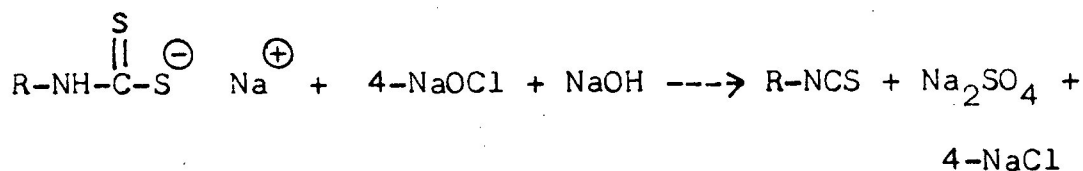


The phosgene method failed to succeed in the preparation of isothiocyanates with electron withdrawing substituents (4-bromophenyl isothiocyanate, *p*-nitrophenyl isothiocyanate, etc.).¹⁷² The decomposition of dithiocarbamates with ethyl¹⁷³⁻¹⁷⁷ or methyl¹⁷⁸ chloroformate (34) produces aliphatic isothiocyanates in very good yields. Reaction takes place via the unstable carbethoxy dithiocarbamate (35) which decomposes into isothiocyanate, carbonyl sulphide and ethanol. Bases, like alkali and triethyl amine, have a catalytic effect on the corresponding decomposition of carbethoxy dithiocarbamate.¹⁷⁹⁻¹⁸¹





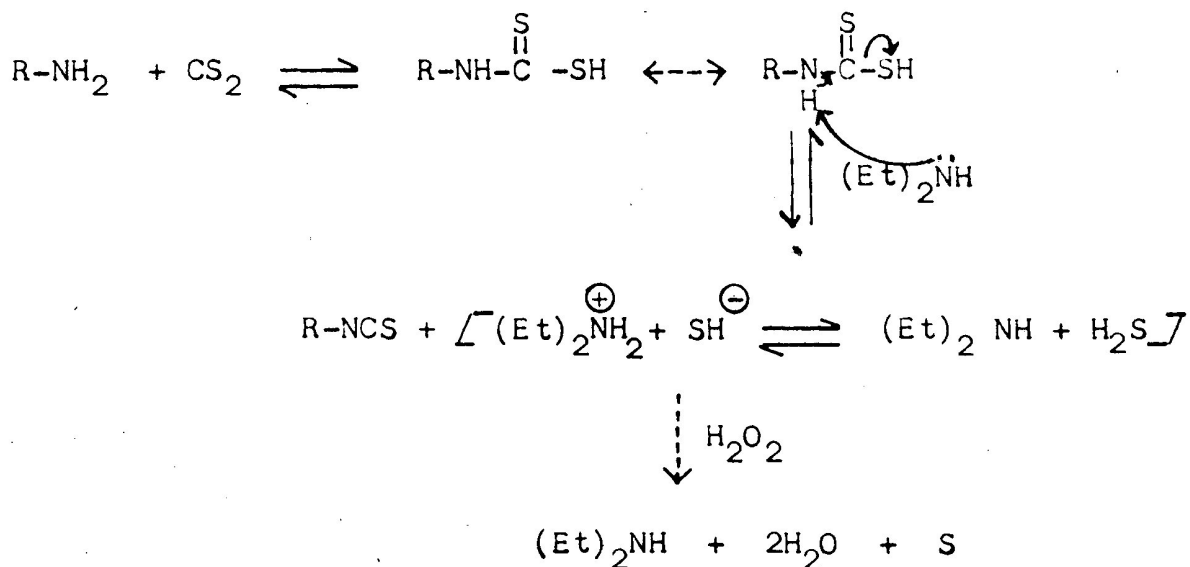
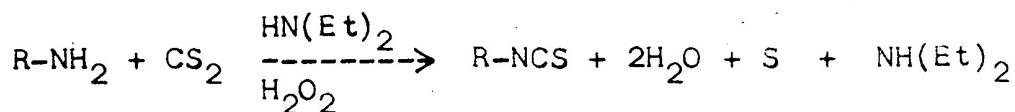
Aliphatic and aromatic isothiocyanates can be prepared by the oxidative decomposition of dithiocarbamates by sodium hypochloride in an alkaline medium.^{182,183}



c) Decomposition by hydrogen peroxide :

A mixture of primary amine and carbon disulfide when treated with hydrogen peroxide in presence of

secondary aliphatic amine produces a rapid exothermic reaction which gives isothiocyanates.¹⁸⁴

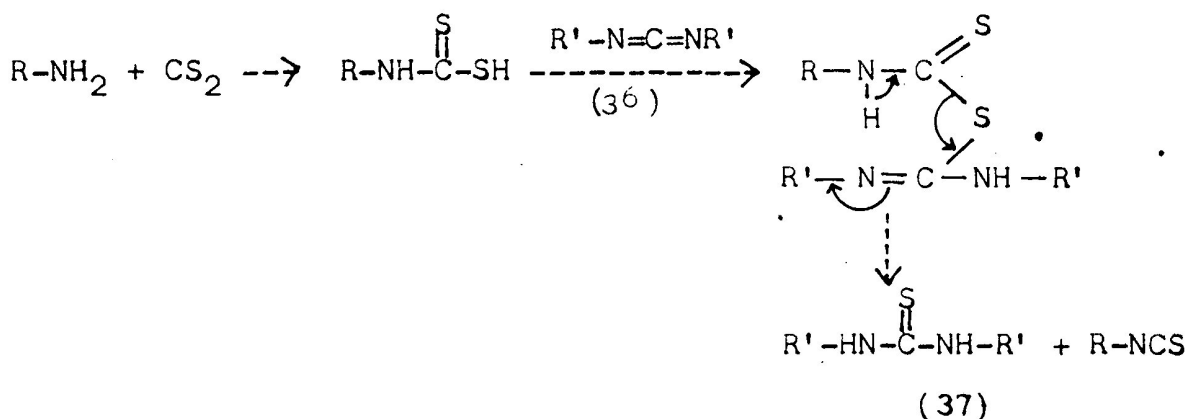


This one-step reaction is suitable for the preparation of aliphatic isothiocyanates. Thioureas are produced as by-products.

d) Decomposition involving carbodimides :

Primary amines react with carbon disulfide and dicyclohexyl carbodiimides (36) in a suitable organic solvent at temperature below 0°C, forming isothiocyanate and 1,3-dicyclohexyl thioureas (37). For the preparation of aliphatic isothiocyanates, ether or tetrahydrofuran¹⁸⁵ proved to be a good solvent. In presence of pyridine or

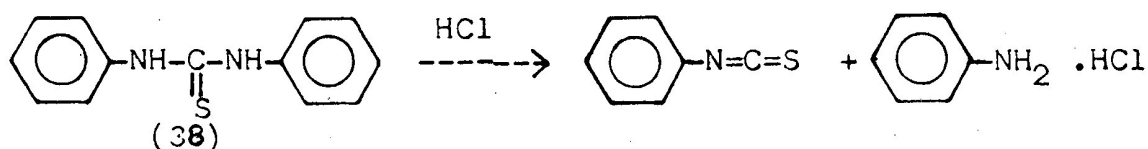
molar equivalent of triethylamine, aromatic primary amines also give good yields of isothiocyanates.¹⁸⁶



R' = Cyclohexyl.

3) Decomposition of Thioureas :

Aromatic isothiocyanates can be prepared by the decomposition of symmetrical diaryl thioureas (38) with acids such as hydrochloric acid,¹⁸⁷⁻¹⁸⁹ sulfuric acid^{190,191} and phosphoric acid. The salt of corresponding arylamine is formed as by-product.¹⁹²



Isothiocyanates are obtained also by the decomposition of N-monoarylthioureas during prolonged heating with chlorobenzene.^{193,194}

EXPERIMENTAL

EXPERIMENTAL

a) p-Butyl phenyl isothiocyanate :

The mixture of p-n-butyl aniline (7.45 g; 0.05 mole), 100 ml acetic acid and hydrochloric acid (40%; 20 ml) was taken in a 500 ml three necked round bottom flask fitted with mechanical stirrer, condenser and dropping funnel. The mixture was stirred in ice-cold condition for 30 minutes. The solution of thiophosgene (5.75 g; 0.05 mole) in chloroform (100 ml) was added dropwise with stirring at constant temperature of 15°C to the above solution. The reaction mixture was stirred further for four hours. The chloroform layer was then separated and washed with water till it was free from acid. The chloroform layer was dried over Na₂SO₄ (anhydrous) and charcoal treatment was given. The excess of chloroform was distilled out at reduced pressure. The residual oil obtained was confirmed by its boiling point.

Yield : 5.15 g (54.0%); b.p._{15mm} 160°C.

(Lit.¹⁴³ b.p._{15mm} 162°C).

b) p-(Butyl)-p'-[4-(2-p-ethoxyanilino-5-methyl)-thiazolyl]-thiocarbanilide :

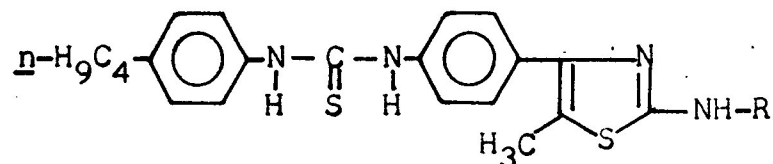
A mixture of 2-(p-ethoxyanilino)-4-(p-aminophenyl)-5-methyl thiazole (1.625 g; 0.005 mole) and p-butylphenyl isothiocyanate (0.575 g; 0.005 mole) in ethanol was taken

and refluxed for four hours. The excess of solvent was removed, when sticky compound was obtained. This compound was triturated in hexane when the solid product was separated. It was filtered and dried. Then recrystallised from benzene.

Yield : 1.84 g (71.2%); m.p. 70°C.

Analysis for $C_{29}H_{32}N_4OS_2$:	<u>% C</u>	<u>% H</u>	<u>% N</u>
Calcd.	67.44	6.20	10.8
Found	67.59	6.33	10.91

All other thiocarbanilide derivatives were prepared by procedure, during the course of this work. Their physical data is summarised in Table-6.

TABLE-6 : p-Butyl-p'-[4'-(2,5-disubstituted thiazolyl)]-thiocarbanilides.

No.	R	Mol. formula	Mol.wt.	M.P. °C	ELEMENTAL ANALYSIS					
					Calcd. %			Found %		
					C	H	N	C	H	N
1.	Phenyl	C ₂₇ H ₂₈ N ₄ S ₂	472	103	68.64	5.93	11.86	69.01	6.23	12.03
2.	p-Chlorophenyl	C ₂₇ H ₂₇ ClN ₄ S ₂	506.5	110	63.96	5.33	11.05	63.71	5.65	11.26
3.	p-Bromophenyl	C ₂₇ H ₂₇ BrN ₄ S ₂	551	95	58.80	4.90	10.16	58.57	5.23	10.31
4.	p-Fluorophenyl	C ₂₇ H ₂₇ FN ₄ S ₂	490	90	66.12	5.51	11.40	66.23	5.63	11.29
5.	2,4-Dichlorophenyl	C ₂₇ H ₂₆ Cl ₂ N ₄ S ₂	541	135	59.88	4.80	10.35	60.21	5.16	10.69
6.	3,4-Dichlorophenyl	C ₂₇ H ₂₆ Cl ₂ N ₄ S ₂	541	95	59.88	4.80	10.35	59.63	4.73	10.41
7.	Phenylethyl	C ₂₉ H ₃₂ N ₄ S ₂	500	80	69.60	6.40	11.20	69.46	6.13	11.45
8.	o-Methoxyphenyl	C ₂₈ H ₃₀ N ₄ OS ₂	502	210	66.93	5.97	11.15	67.02	6.15	11.40
9.	p-Methoxyphenyl	C ₂₈ H ₃₀ N ₄ OS ₂	502	75	66.93	5.97	11.15	66.87	5.77	10.89
10.	o-Ethoxyphenyl	C ₂₉ H ₃₂ N ₄ OS ₂	516	85	67.44	6.20	10.80	67.06	6.17	10.67
11.	p-Ethoxyphenyl	C ₂₉ H ₃₂ N ₄ OS ₂	516	70	67.44	6.20	10.80	67.59	6.33	10.91
12.	Benzyl	C ₂₈ H ₃₀ N ₄ S ₂	486	87	69.13	6.17	11.52	68.91	6.23	11.61
13.	3-Methyl-2-Pyridyl	C ₂₇ H ₂₉ N ₅ S ₂	487	75	66.50	5.95	14.37	66.74	6.07	14.50
14.	2-Furylmethyl	C ₂₆ H ₂₈ N ₄ OS ₂	476	85	65.54	5.88	11.76	65.67	5.75	11.39

PART IV

RESULTS AND DISCUSSION

BIOLOGICAL SCREENING RESULTS AND DISCUSSION

Antitubercular agents used currently for the tuberculosis, for their effectiveness depend upon their capacity to inhibit the multiplication of or kill, the invading microorganisms Mycobacterium tuberculosis under the conditions which exist in vivo.

Two major lines of approach are available for finding new antimicrobial agents. First by studying the metabolism of the microorganisms, a compound may be prepared which will specifically interfere with their metabolism to the point where multiplication will cease. Secondly by exploring a wide variety of substances and determining their ability to inhibit the multiplication of M. tuberculosis in vivo and focus attention only on those active drugs which seem better for administration to human beings. This empirical type of mass screening has been most successful in producing chemotherapeutic agents of clinical usefulness.

In practical consideration direct in vivo screening has certain limitations. First relatively few compounds can be tested per unit of time. Second, the amount of drug sample required is large, frequently exceeding the amount immediately available, thus limiting the number and types of compounds which can be tested.

It is, therefore, desired to have a test which could be more simply and rapidly performed and which would require only a small amount of drug. These requirements are best fulfilled by in vitro bacteriostatic test.

SCREENING PROCEDURE

In vitro antitubercular testing was carried out against the human virulent strain of Mycobacterium tuberculosis (H₃₇Rv) by the method of disperse culture technique using Kirchner's medium containing Tween-80 as described by Rake et al.¹⁹⁵

Sterile Kirchner's media (4.4 ml) was dispensed in each borosilicate test tube (150 x 20 mm). The compounds (10 mg) under test were dissolved in 10 ml solvent such as dimethyl formamide (DMF), dilute HCl, ethanol, etc. as the case may be.

The serial drug dilutions were made in such a way as to give final concentrations of 200, 100, 50, 25, 12.5, 6.25 ug/ml, etc. Sterile normal bovine serum (0.5 ml) was added to each test tube containing certain drug concentration. The 0.1 ml inoculum of standard suspension of *M. tuberculosis* (H₃₇Rv) containing 10⁶ bacilli/ml was added at the end. The tubes were incubated at 37°C for seven to eight days and then examined for the presence or

absence of the growth of the test organisms. The lowest concentration which showed no visible growth was taken as an end point.

Control tubes with INH (Isonicotinic hydrazide) and ethambutol at concentrations 0.04 $\mu\text{g/ml}$ and 0.1 $\mu\text{g/ml}$ and tubes without any drugs were taken for comparison. The solvents that were used for dissolving the substances under study were also tested to see that, they did not affect the growth at the concentrations, used under these experimental conditions.

RESULTS AND DISCUSSION

Fifty-two compounds were synthesized and subjected for their in vitro antitubercular screening. Most of the compounds have shown minimum inhibition concentration (MIC) against M. tuberculosis in the range 25 $\mu\text{g/ml}$ to 1.5 $\mu\text{g/ml}$.

The compounds (1-10) from Table 1, 2-(substituted-aryl/heterocyclic)-4-(N,N-diethyl-N'-phenyl urea) thiazoles exhibited activity at concentration ranging from 6.125 $\mu\text{g/ml}$ to 0.39 $\mu\text{g/ml}$. Compound No.3, 2-(p-methoxyphenyl)-4-(N,N-diethyl-N'-phenyl urea) thiazole was found to be most active among these compounds, with MIC 0.39 $\mu\text{g/ml}$. 5-Bromo-vanillino derivative (No.5) was active at 0.78 $\mu\text{g/ml}$. Heterocyclic substitution like 3-pyridyl and 4-pyridyl in

compound Nos. 8 and 9 exhibited better activity at concentration 1.56 $\mu\text{g/ml}$. Benzyl derivative (No. 2) was more active than phenyl derivative (No.1) of the same series.

The compounds, 2-(substituted anilino/heterocyclic amino)-4-(N,N-diethyl-N'-phenyl urea) thiazoles tabulated in Table 2 had activity in the range of 25 $\mu\text{g/ml}$ to 1.56 $\mu\text{g/ml}$.

The activity of compounds was found to be increased when phenyl group was taken away from thiazole nucleus at position 2, with the addition of carbon atom in straight chain. This was indicated as 2-phenylethyl derivative (No.8) being more active than benzyl derivative (No.6) and phenyl derivative (No.1) less active than benzyl derivative (No.6). However, branched chained 1-phenylethyl-derivative (No.7, Table 2) was inactive as antitubercular at concentrations used for testing.

Monohalo-substituted phenyl ring present at 2nd position of thiazole ring, imparts better activity, where p-chlorophenyl derivative (No.2, Table 2) being most active among other halogen derivatives. Surprisingly, the dihalogen substitution like 2,4-dichlorophenyl derivative (No.5) was found to be inactive. p-Alkoxyphenyl deri-

vatives (Nos. 9-12) have shown moderate activities in the range 12.5 $\mu\text{g/ml}$ to 3.125 $\mu\text{g/ml}$.

3-Methyl-2-pyridyl (No.13) and 2-furylmethyl (No.14) derivatives were active at concentrations 3.1 $\mu\text{g/ml}$ and 1.5 $\mu\text{g/ml}$, respectively.

According to Kulkarni et al.⁵⁰ the antitubercular activity of the thiazole increases if methyl group is introduced at its 5th position. However, after biological screening of compounds it was found that compounds (1-14), from Table 3, 2-(substituted anilino/heterocyclic amino)-4-(N,N-diethyl-N'-phenyl urea)-5-methyl thiazoles did not show any marked increase in the activity than the compounds from Table 2, which do not contain methyl group at 5th position of thiazole. In this series of compounds, (from Table 3) the activity of phenyl (No.1), benzyl (No.7) and phenylethyl (No.8) derivatives was in increasing order. Among p-halophenyl derivatives of thiazole p-chlorophenyl derivative (No.2) was most active with MIC 1.5 $\mu\text{g/ml}$. Alkoxy phenyl derivatives (Nos. 9-12) showed moderate activity in the range 100 $\mu\text{g/ml}$ to 1.5 $\mu\text{g/ml}$.

Compound Nos. 13 and 14 containing heterocyclic amino substitution at position 2 and methyl group at 5 position showed activities exactly similar to compounds 13 and 14 from Table 2.

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Compounds (1-14) from Table 4, *p*-butyl-*p'*-[4-(2,5-disubstituted)thiazolyl]thiocarbanilides showed activity in the concentration range of 100 μ g/ml to 3.12 μ g/ml. 2-Phenylethyl derivative (No.8) was active than phenyl derivative (No.1) but benzyl derivative (No.7) was inactive at 200 μ g/ml. The activity of *p*-chloro (No.2) *p*-bromo (No.3) and *p*-fluorophenyl derivative (No.4) was found to be in increasing order. 2-Furylmethyl derivative (No.14) showed no activity at 200 μ g/ml; however, compound No. 13 containing 3-methyl-2-pyridyl substitution was active at 3.12 μ g/ml.

From the above biological screening results, some interesting features have been noted. These are -

1) Introduction of amino (-NH-) linkage at position 2 of thiazole ring and methyl (-CH₃) group at 5th position of thiazole derivatives, studied here, did not show any improvement in their in vitro antitubercular activity.

2) All the thiazole derivatives substituted by alkoxy phenyl/alkoxy phenyl amino group at position 2, were found to be active at the concentrations used for testing.

3) Amongst the four series of compounds, studied here, the order of activities of phenyl, benzyl and phenyl-

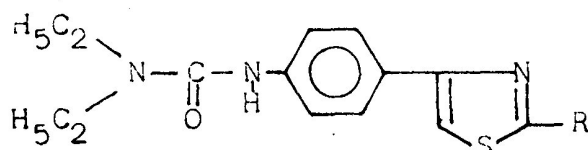
ethyl derivatives was found to be increasing such as phenylethyl > benzyl > phenyl except in the last series of thiocarbanilides where the benzyl derivative was found to be inactive.

4) All the thiazole derivatives substituted with *p*-halogen phenyl compounds at position 2 were active. The order of activities of these compounds was chloro > bromo > fluoro in the first three series. However, in case of the compounds from Table 4, the activity was in the decreasing order of fluoro > bromo > chloro.

5). Of all the fifty-two compounds synthesised, the compound 2-(*p*-methoxyphenyl)-4-(*N,N*-diethyl-*N'*-phenyl-urea)thiazole was found to be most active at 0.39 µg/ml. This activity is comparable to that of paraamino salicylic acid (PAS), a standard drug with MIC 0.4 µg/ml.

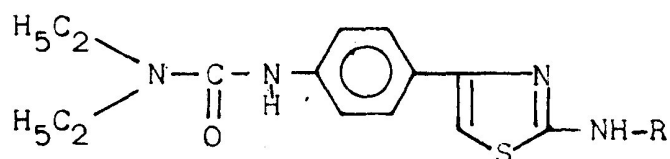


TABLE-1 : 2-(Alkyl/substituted-phenyl/heterocyclic)-4-
(N,N.diethyl-N'-phenyl urea) thiazole



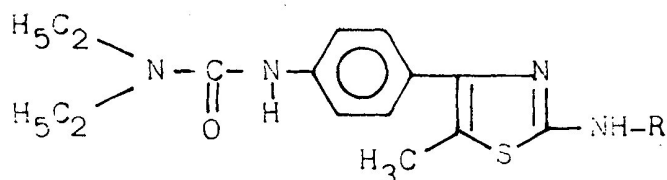
No.	R	Antitubercular activity (μ g/ml)
1.	Phenyl	6.25
2.	Benzyl	1.50
3.	p-Methoxyphenyl	0.39
4.	3-Methoxy-4-propoxyphenyl	3.125
5.	5-Bromovanillino	0.78
6.	2,3-Dichlorophenoxy aceto	3.125
7.	N,N-Dimethylamino phenyl	1.56
8.	3-Pyridyl	1.56
9.	4-Pyridyl	1.56
10.	Methyl	3.125

TABLE-2. : 2-(Substituted anilino/heterocyclic amino)-
4-(N,N-diethyl-N'-phenyl urea) thiazole



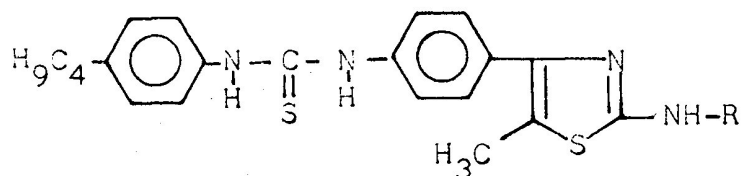
No.	R	Antitubercular Activity ($\mu\text{g/ml}$)
1.	Phenyl	25
2.	<i>p</i> -Chlorophenyl	1.56
3.	<i>p</i> -Bromophenyl	3.12
4.	<i>p</i> -Fluorophenyl	6.25
5.	2,4-Dichlorophenyl	Inactive at 200 $\mu\text{g/ml}$
6.	Benzyl	3.125
7.	1-Phenylethyl	Inactive at 200 $\mu\text{g/ml}$
8.	2-Phenylethyl	1.56
9.	<i>o</i> -Methoxyphenyl	3.125
10.	<i>p</i> -Methoxyphenyl	12.5
11.	<i>o</i> -Ethoxyphenyl	6.25
12.	<i>p</i> -Ethoxyphenyl	3.125
13.	3-Methyl-2-pyridyl	3.125
14.	2-Furylmethyl	1.56

TABLE-3 : 2-(Substituted-anilino/heterocyclic-amino)-
4-(N,N-diethyl-N'-phenyl-urea)-5-methyl-
thiazole



No.	R	Antitubercular Activity (μ g/ml)
1.	Phenyl	50
2.	<i>p</i> -Chlorophenyl	1.56
3.	<i>p</i> -Bromophenyl	50
4.	<i>p</i> -Fluorophenyl	3.125
5.	2,4-Dichlorophenyl	50
6.	3,4-Dichlorophenyl	1.56
7.	Benzyl	25
8.	Phenylethyl	1.56
9.	<i>o</i> -Methoxyphenyl	100
10.	<i>p</i> -Methoxyphenyl	3.125
11.	<i>o</i> -Ethoxyphenyl	1.56
12.	<i>p</i> -Ethoxyphenyl	12.5
13.	3-Methyl-2-pyridyl	3.125
14.	2-Furylmethyl	1.56

TABLE-4 : p-Butyl-p'-[4-(2-substituted-anilino-5-methyl) thiazolyl]-thiocarbanilide .



No.	R	Antitubercular Activity ($\mu\text{g/ml}$)
1.	Phenyl	25
2.	p-Chlorophenyl	100
3.	p-Bromophenyl	25
4.	p-Fluorophenyl	3.12
5.	2,4-Dichlorophenyl	25
6.	3,4-Dichlorophenyl	100
7.	Benzyl	Inactive at 200 $\mu\text{g/ml}$
8.	Phenylethyl	6.25
9.	o-Methoxyphenyl	12.5
10.	p-Methoxyphenyl	6.25
11.	o-Ethoxyphenyl	12.5
12.	p-Ethoxyphenyl	25
13.	3-Methyl-2-pyridyl	3.12
14.	2-Furylmethyl	Inactive at 200 $\mu\text{g/ml}$

standard PAS = 0.4 $\mu\text{g/ml}$.

SPECTROSCOPIC METHOD OF ANALYSIS

SPECTROSCOPIC METHOD OF ANALYSIS

Infrared spectroscopy is the most versatile, highly efficient and important technique for solving the problems relating to structural elucidation of organic molecules without the tiresome evaluative method.

It would not be an exaggeration if stated that infrared spectroscopy is the most powerful physical method employed by chemists. Other physical methods such as the X-ray diffraction and electron diffraction, gives structural information on molecules only after intricate and time consuming analysis.

The region between $1430-910\text{ cm}^{-1}$ in infrared spectrum is particularly rich in absorption bands. No two different molecules have the same set of absorption bands in this region. Although similar molecules may show similar spectra, there will almost always be noticeable differences in this region. For this reason, the range between $1430-910\text{ cm}^{-1}$ is commonly referred to as the finger print region.

The compounds synthesized in the present investigation have been characterized by the group frequencies as given in Tables 1 and 2.

Thiazole ring :

The characteristic patterns of absorption of the ring stretching vibrations of 5-membered rings (such as thiazole) probably result from the complete interaction of the C=C and C=N vibrations and it is, therefore, very difficult to isolate the different vibrations. The ring stretching vibrations of the thiazole gives rise to absorption bands in the 1615 cm^{-1} and 1485 cm^{-1} region¹⁹⁶ of the IR spectrum.

Secondary amine :

The secondary amines show a single N-H stretching band in the $3500\text{--}3100\text{ cm}^{-1}$ region.¹⁹⁷

Alkanes :

a) n-butyl group :

A hydrocarbon containing a methyl group (as in n-butyl) usually shows two distinct bands, one at 2960 cm^{-1} and the other at 2870 cm^{-1} which is due to the asymmetric and symmetric stretching of the methyl group respectively.¹⁹⁸

b) n-Ethyl group :

The n-ethyl group exhibits two absorption bands, the first being a strong band in the region between $3000\text{--}2900\text{ cm}^{-1}$ and the second, a band of medium intensity, in the region between $2900\text{--}2800\text{ cm}^{-1}$.¹⁹⁹

c) Methylene group :

The methylene group shows a strong absorption band in the region between $1525-1475\text{ cm}^{-1}$. 199

Substituted aromatic ring system :

a) 1,4-Disubstituted benzene ring :

The 1,4-substitution on the benzene ring is identified by strong bands in the region $1125-1050\text{ cm}^{-1}$ and $860-800\text{ cm}^{-1}$. 197

b) Monosubstituted benzene ring :

The monosubstituted benzene ring is characterized by absorption bands in two regions viz., $1525-1475\text{ cm}^{-1}$ and $800-700\text{ cm}^{-1}$. 199,200

Thiocarbonyl group :

The thiocarbonyl group which is linked to nitrogen exhibits two absorption bands of medium intensity. The first band is found in the $1525-1425\text{ cm}^{-1}$ region, while the second occurs in the $1300-1075\text{ cm}^{-1}$ region.

2-Substituted furan :

The ring stretching vibration of 2-substituted-furan is observed in the region between $1400-1380\text{ cm}^{-1}$. 196

Carbonyl group :

If a compound contains a carbonyl group, the absorption caused by C=O stretching is generally among the strongest present. The carbonyl frequency of several series of secondary amides have been studied and the frequency of absorption is quoted to be falling close to 1650 cm^{-1} .²⁰² Generally, the absorption frequencies lie between $1680\text{--}1625\text{ cm}^{-1}$.

Experimental data :

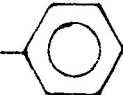
The compounds synthesized in the present investigation have been analysed by the KBr-pellet technique. Spectral grade potassium bromide was used for this purpose. All infrared spectra were recorded on a Perkin-Elmer 257 grating Infrared Spectrophotometer.

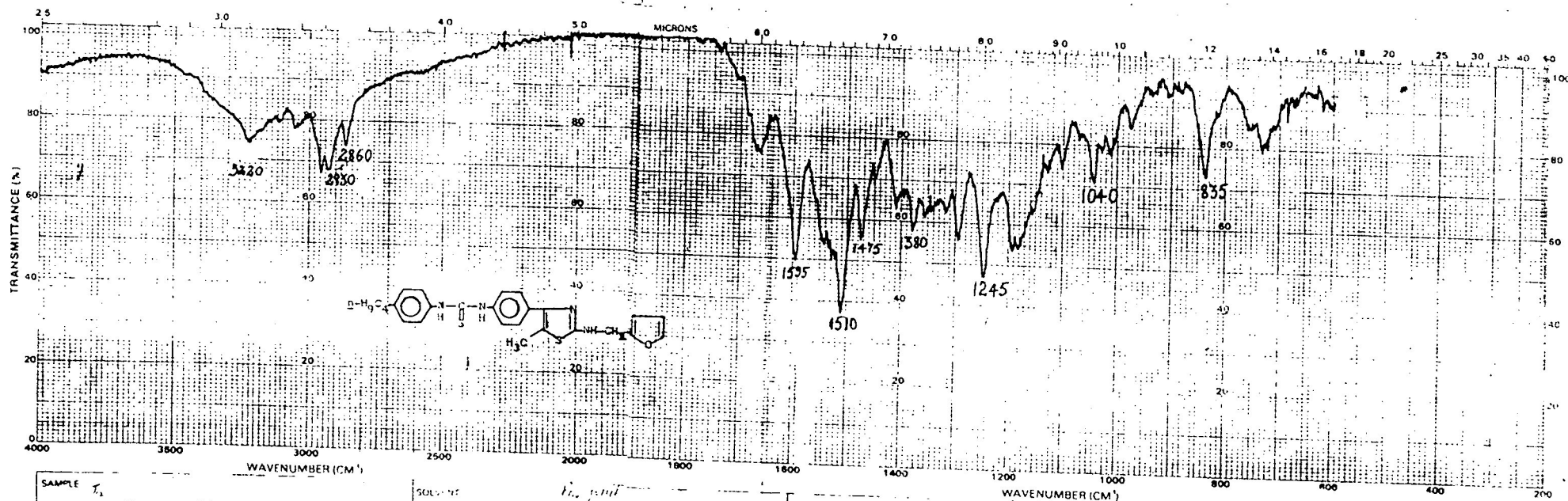


TABLE-1

Compd. No.		Thiazole	Secondary amine	n-C ₄ H ₉	1,4-Disub- stituted benzene ring	Thiocarbonyl N-C=S group	2-Substi- tuted- furan	Mono- substituted benzene ring.		
	Reqd cm ⁻¹	1615 1485	3500- 3100	2960 2870	1125- 1050	860- 800	1525- 1425	1300- 1075	1400- 1380	1525- 800- 1475 700
1		1595 1475	3220	2930 2860	1040	835	1510	1245	1380	- -
2		1585 1470	3160	2920 2860	1045	840	1520	1240	-	- -
3		1590 1460	3380	2920 2860	1050	850	1575	-	-	- -
4		1590 1470	3220	2920 2840	1045	840	1510	1245	-	- -
5		- 1450	3200	2920 2840	-	840	1500	-	-	- -
6		1580 1440	3220	2920 2860	1040	840	1510	1245	-	1530 760, 710

TABLE-2

Compd. No.		Thiazole	Secondary amine	n-C ₂ H ₅		1,4-Disubsti- tuted benzene ring 		Carbonyl group HN-C=O	Methylene group -CH ₂ -	Monosubstituted benzene ring 	
	Reqd. cm ⁻¹	1615 1485	3500- 3100	3000- 2900	2900- 2800	1125- 1050	860- 800	1680- 1625	1525- 1425	1525- 1475	800- 700
7		1585 1485	3300	2950	2800	1060	850	1640	1450	1540	760, 720



SAMPLE *T₂*
 ORIGIN *Perkin Elmer Lab*

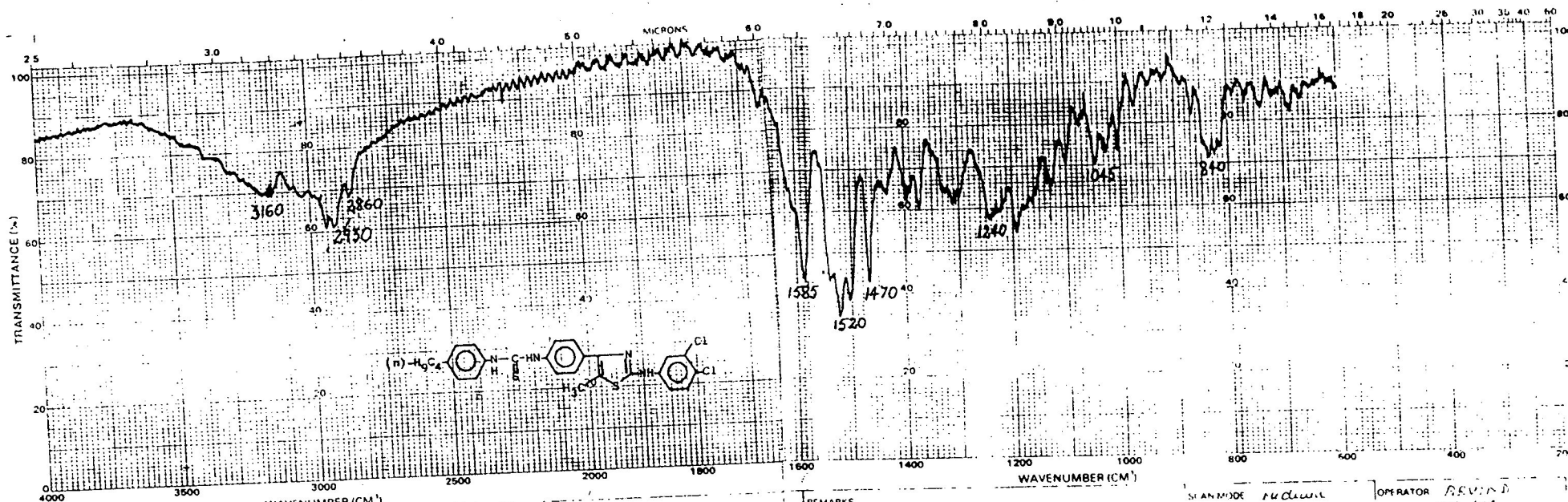
SOLVENT
 CONCENTRATION
 CELL PATH
 REFERENCE

in part

REMARKS

SCAN MODE *Normal*
 SLIT *Normal* TIME CONSTANT
 PERKIN ELMER
 PART NO. 5100 4367

OPERATOR *J. J. ...*
 DATE *2/17/27*
 REF NO *1*



SAMPLE *T₁₁*

ORIGIN

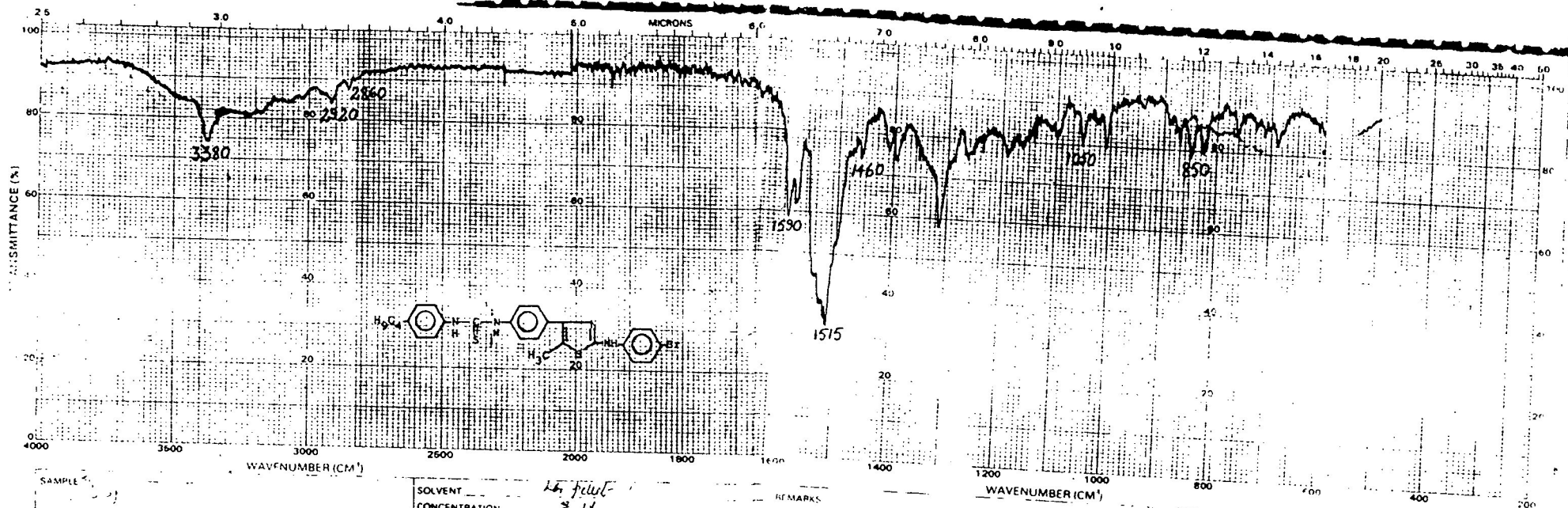
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

kBr pellet
1% approx

REMARKS

SCAN MODE *normal*
SLIT *normal* TIME CONSTANT
PERKIN ELMER
PART NO 5100 4367

OPERATOR *REVIND*
DATE *12/1/50*
REF NO *11*



SAMPLE
ORIGIN

SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

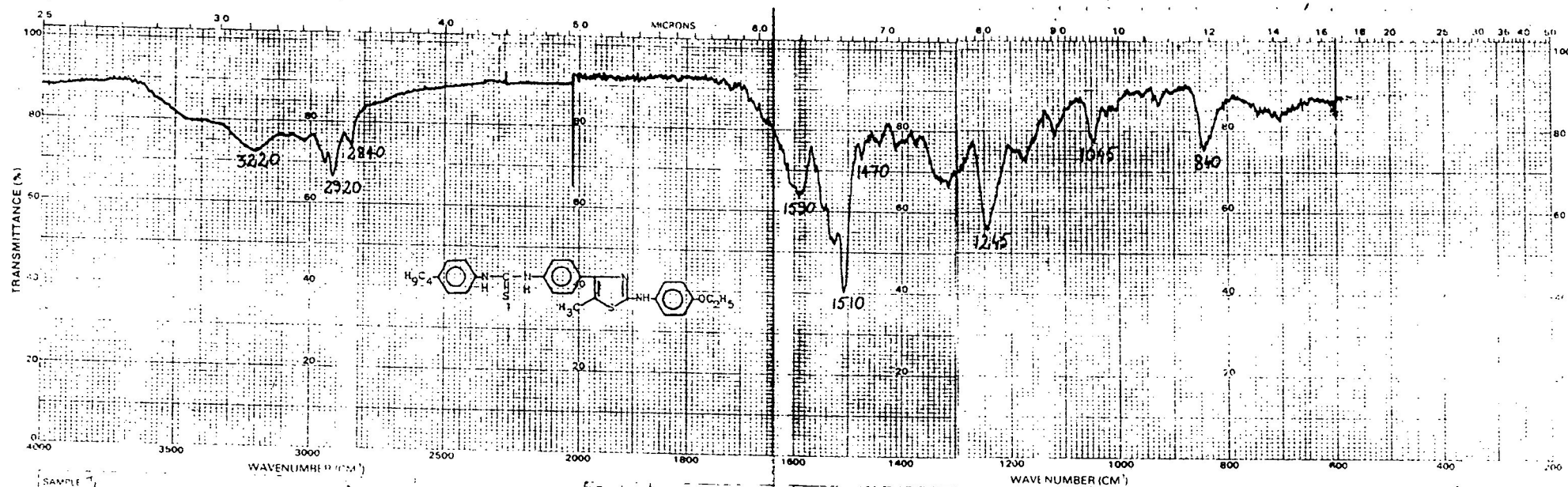
1.5 ml
2.16

REMARKS

WAVENUMBER (CM⁻¹)

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SLIT *1/2 mm* (SAME CONSTANT)
PERKIN ELMER
PART NO. 5106 4367

OPERATOR *H. Lind*
DATE *4/11/19*
REF NO *(3)*



SAMPLE 7
ORIGIN

SOLVENT	CONCENTRATION	CELL PATH	REFERENCE
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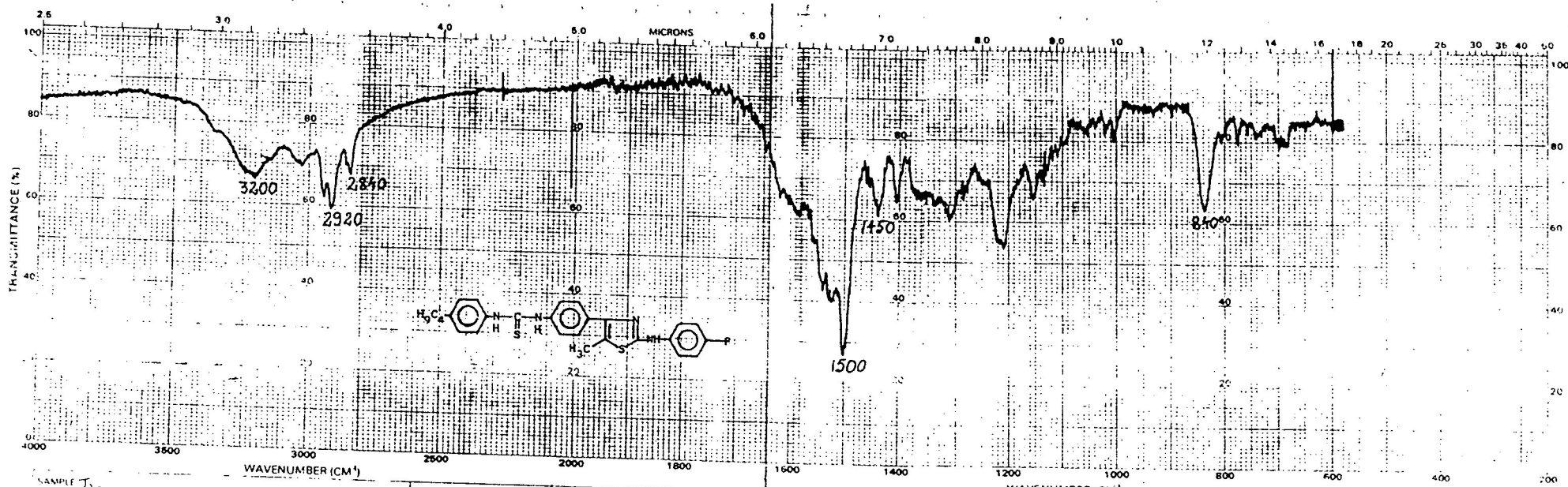
his point
= 1/2.

REMARKS

SCAN MODE *Normal*
SLIT *1.5mm* TIME CONSTANT
PERKIN ELMER
PART NO 5100 4167

OPERATOR	
DATE	
REF NO	

126



SAMPLE *J₂*

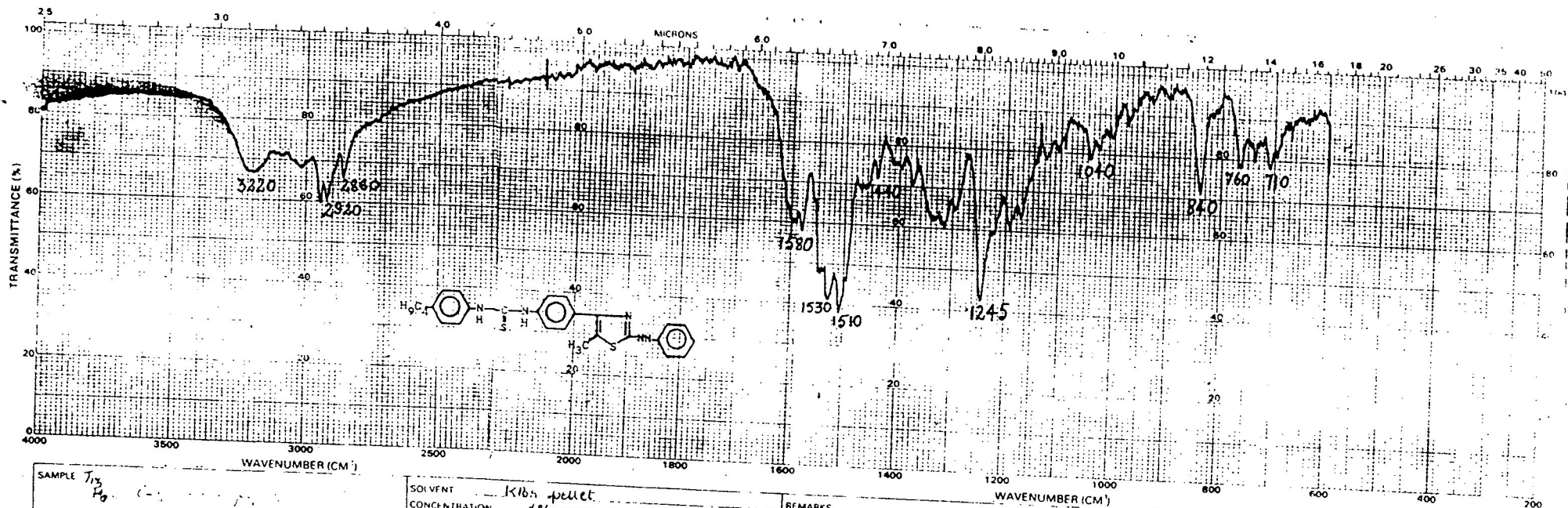
ORIGIN

SOLVENT *in fluid*
 CONCENTRATION *1.6*
 CELL PATH
 REFERENCE

REMARKS

SCAN MODE *ADDM*
 SLIT *1mm* TIME CONSTANT
 PERKIN ELMER
 PART NO 5100 4367

OPERATOR *J. H. D.*
 DATE *2/1/79*
 REF NO *(5)*



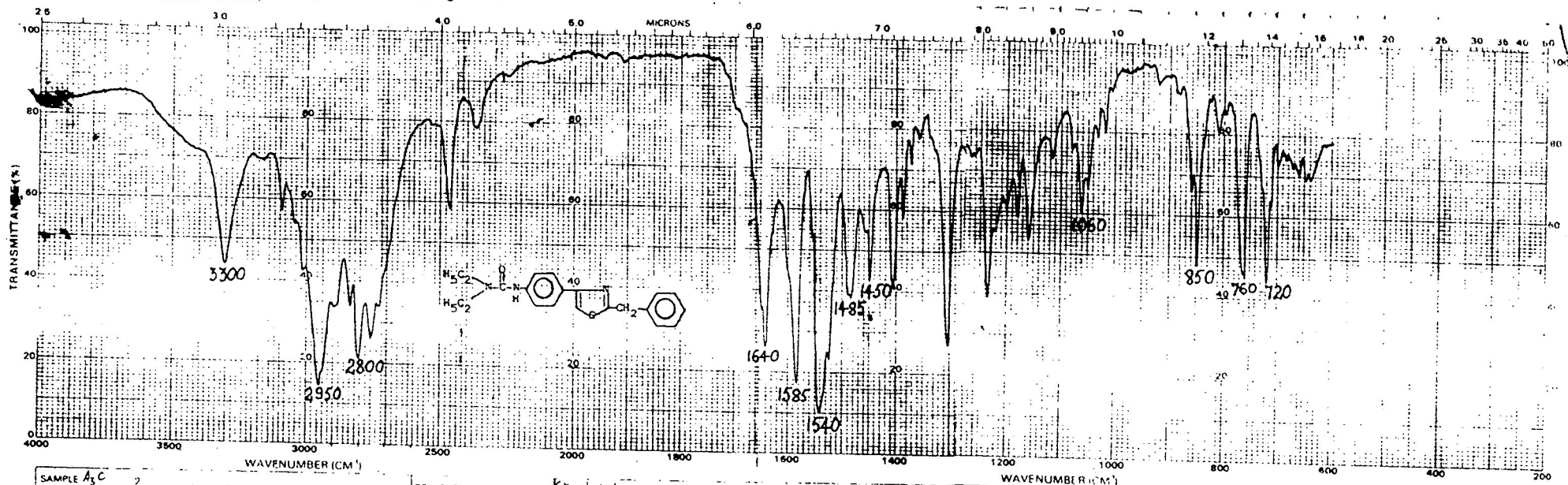
SAMPLE *T₁₃*
P₉
 ORIGIN

SOLVENT *KBr pellet*
 CONCENTRATION *1% approx*
 CELL PATH
 REFERENCE

REMARKS

SCAN MODE *medium*
 SLIT/PM/RT/TIME CONSTANT
 PERKIN ELMER
 PART NO. 5100 #361

OPERATOR *RFVIND*
 DATE *10/11/89*
 REF NO *112 (6)*



SAMPLE *A5C*
4-ethyl-2,5-dimethyl-3-nitrobenzoic acid
 ORIGIN

SOLVENT
 CONCENTRATION
 CELL PATH
 REFERENCE

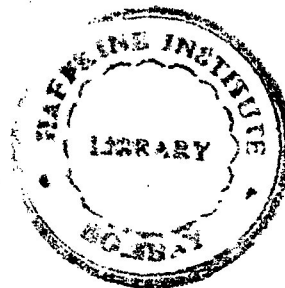
kb. fluid
8.2

REMARKS

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 PERKIN ELMER
 PART NO 5100 4362

OPERATOR *Flann*
 DATE *3/11/79*
 REF NO *①*

S U M M A R Y



S U M M A R Y

In spite of the continuous efforts to eliminate tuberculosis, on world-wide basis, it continues to be a scourge among the people of the third world. Immunization and chemotherapy are two major weapons, to fight against this disease. Immunization helps in prevention of the disease; whereas, chemotherapy cures the disease. Various chemotherapeutic agents have been developed to treat T.B.; however, due to resistance and toxicity problems, there is the need for search of more effective and less toxic agents. This thesis enumerates the efforts made in this direction.

Some thiazole derivatives have been studied for their chemistry, experimental and biological aspects in this work. The entire study carried out during the course of research work is divided into four parts.

The Part I starts with 'Introduction', where the disease from the point of view of biology of its etiological agent, epidemiology, efforts to eliminate it on worldwide basis and chemotherapy have been described in brief. This is followed by "Review of Literature" which gives an account of antitubercular agents available today. The first part ends with the "Plan of Work" which gives the guide-lines for the proposed work.

Part II covers the chemistry aspect of synthesis and various experimental procedures in the field of thioamides and thioureas which are intermediates for the synthesis of thiazoles. This part is divided into 2 sections - Section A covers thioamides and Section B contains thioureas.

Part III describes chemistry and experimental procedures of the synthetic work carried out during the course of research work. This part includes Section A to Section D.

The first series under Section A deals with synthetic aspects of 2-(alkyl/substituted-phenyl/heterocyclic)-4-(N,N-diethyl-N'-phenyl urea) thiazole. In this section chemistry and various synthetic methods for thiazole derivatives have been discussed in detail. The thiazole nucleus was obtained by condensation of p-amino phenacyl chloride with different substituted thioamides. The 2-substituted-4-(p-aminophenyl)thiazole thus obtained was condensed with N,N-diethyl carbamoyl chloride to give the final compound.

The Section B comprises 2-(substituted-anilino/heterocyclic-amino)-4-(N,N-diethyl-N'-phenyl-urea)thiazole. The 2-substituted-anilino thiazoles were prepared by refluxing together p-amino phenacyl chloride and different monosubstituted thioureas in alcohol.

2-(Substituted-anilino/heterocyclic amino)-4-(N,N-diethyl-N'-phenyl urea)-5-methyl thiazoles have been discussed in Section C. The 2,4-disubstituted-5-methyl thiazole was prepared by condensing α -chloro-p-amino-propiophenone and monosubstituted thioureas in alcohol. α -Chloro-p-amino-propiophenone was prepared by Friedel-Craft's reaction.

Section D covers p-(butylphenyl)-p'-[4-(2,5-disubstituted)thiazolyl]-7-thiocarbanilides. Thiocarbanilide was prepared by condensation of 2,5-disubstituted-4-(p-aminophenyl)thiazole and p-butylphenyl isothiocyanate. The p-butylphenyl isothiocyanate was prepared by reaction between p-butyl aniline and thiophosgene. Various methods for preparation of isothiocyanates have also been discussed.

Part IV describes the method used for in vitro antitubercular screening against Mycobacterium tuberculosis. Structure activity relationship is discussed in detail. It revealed that among the fifty-two compounds synthesized the most active was 2-(p-methoxyphenyl)-4-(N,N-diethyl-N'-phenyl-urea)thiazole with minimum inhibition concentration at 0.39 $\mu\text{g/ml}$.

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SYNOPSIS

A SYNOPSIS OF THE THESIS
SUBMITTED TO
THE UNIVERSITY OF BOMBAY
FOR
THE DEGREE OF MASTER OF PHARMACY

.....

TITLE OF THE THESIS : "SYNTHESES AND STUDY OF SOME
THIAZOLE DERIVATIVES AS POSSIBLE
ANTITUBERCULAR AGENTS"

NAME OF THE CANDIDATE : MISS SRAGDHARA VISHWANATH NALAVDE.

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S Y N O P S I S

Tuberculosis is a communicable disease of long standing, which has been successfully controlled by most of the developed countries, but continues to contribute significantly to morbidity and mortality in the developing countries.¹

Even today, when incidence of tuberculosis in the western nations has markedly decreased and the mortality is less than ten per hundred thousand population, tuberculosis still remains one of the most prevalent infectious diseases. It has been estimated that about 8-10 million cases of tuberculosis are prevalent on world-wide basis and of this, 80 percent in the developing countries.² In India nearly 5,00,000 persons die of tuberculosis annually. The number of patients at any given time has been estimated to be at least 9-10 million, of which one-fourth (2-2.5 million) are likely to bear the infectious type.¹

Widely different chemical designs represent optimum therapy for all forms of diseases, caused by the sensitive strains of Mycobacterium tuberculosis. The first choice of drugs constitutes the greatest level of

efficiency with an acceptable degree of toxicity. These agents include isoniazide, rifampicin, ethambutol and streptomycin. Due to resistance problems and patient related factors physicians were compelled to use "second line" of drugs such as pyrazinamide, ethionamide, para-aminosalicylic acid (PAS), kanamycin, capreomycin and cycloserine.

However, there is a continuous need to search for new and better drugs with higher efficacy and lower toxicity, than those currently available. The biochemical mechanism of the already existing drugs is used as a basis for designing new and better weapons to fight against the mycobacterial disease. Isoniazide is proposed to act as antitubercular agent by interfering with NAD (Nicotinamide Adenine Dinucleotide) and NADP (Nicotinamide Adenine Dinucleotide phosphate) which are dehydrogenase cofactors in microorganisms.³ Isoniazide contains a pyridine ring. It is well known that thiazole ring is isosteric (having similar electronic and steric configuration) with pyridine ring.⁴ Hence, thiazole moiety may have same mechanism of action against tubercle bacilli similar to that of isoniazide. Therefore, thiazole nucleus was selected for study.

Since last decade our laboratory is engaged in the

investigation of antitubercular activity in different 2,4-disubstituted thiazole derivatives. The biological screening data reveals that this synthetic chemical lead deserves special medicinal attention for further exploitation in tuberculosis therapy. Accounts of our efforts in this direction is the subject matter of this thesis.

The thesis will consist of 'Introduction', 'Review of Literature' and 'Plan of Work' in Part I. Further, it will be divided into different parts as briefly described here.

PART - II

This part mainly deals with chemistry and preparation of different substituted thioamides and substituted thioureas, which play an important role in the preparation of different 2,4-disubstituted thiazoles. It is divided into Section-A and Section-B.

Section - A

Introduction, chemistry and preparation of different thioamides.

Section - B

Introduction, chemistry and preparation of different thioureas.

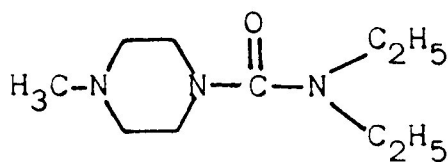
PART - III

This part comprises different substituted thiazoles and it is divided into Sections A to D.

Section - A

Synthesis of 2-(substituted-phenyl/heterocyclic)-4-(N,N-diethyl-N'-phenyl urea) thiazole :

N,N-Diethyl carbamazepine (Hetzaran) (I) by Lederle Lab., U.S.A.⁵ contains N,N-diethyl carbamoyl linkage and it is a well established drug used for antifilarial activity.



(I)

The activity is due to the N,N-diethyl carbamoyl linkage.⁵

In continuation of the work done during the last decade, Prabhu et al.⁶ have published a paper on 2,4-disubstituted thiazole (II) which has shown good response against tubercular bacilli. The peculiarity in this series was that they were active only against M. tuberculosis bacteria.

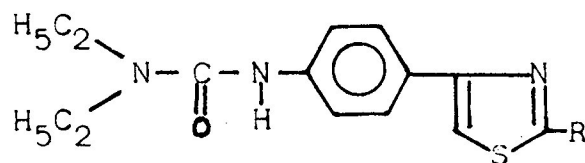


(II)

where, R = Alkyl, aryl;

R' = 2-Pyrazinyl, 5'-nitro-2-furyl,
1-adamantyl.

Taking in view the above facts about N,N-diethyl carbamoyl linkage and already knowing the well documented facts about biological nature of the thiazole nucleus, it was thought worthwhile to synthesize the compact organic molecule containing, 2,4-disubstituted thiazole and N,N-diethyl carbamoyl linkage in it. Accordingly, ten compounds have been prepared and tested for their anti-tubercular activity. The general structure of this thiazole is as shown below (III).



(III)

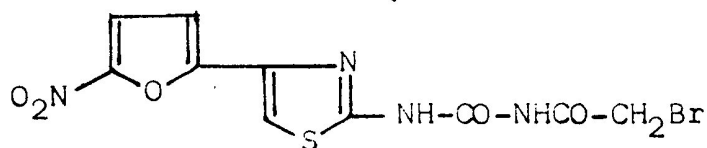
where, R = Methyl, substituted-aryl, etc.

Section - B

2-(Substituted-anilino/heterocyclic amino)-4-(N,N-diethyl-N'-phenyl-urea)thiazole :

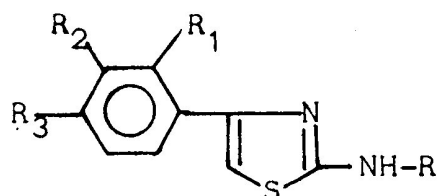
Closier et al.⁷ from Park-Davis Company, England while synthesizing different 2,4-disubstituted thiazoles

succeeded in synthesizing compound (IV) exhibiting high in vitro antibacterial activity against Streptococcus aureus and M. tuberculosis at concentrations of 0.08 $\mu\text{g/ml}$ and 20 $\mu\text{g/ml}$.



(IV)

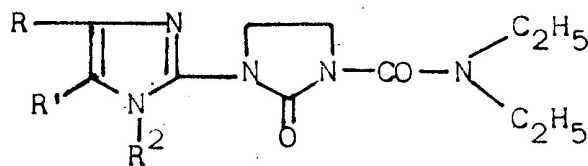
Substituted thiazoles are reported as promising chemotherapeutic antiviral agents. Among them Grafe et al.⁸ reported 4-(substituted-phenyl)-2-(substituted-amino) thiazoles as antiviral agents (V).



(V)

where, $R = \text{H, Me, Pr}$; $R_1 = \text{H, Me}$;
 $R_2, R_3 = \text{H, Cl, OMe}$.

Nagarajan et al.⁹ from Ciba-Geigy A.G. have published data on the imidazole moiety (VI) containing N,N-diethyl carbamoyl linkage as bactericide and protozoacide.

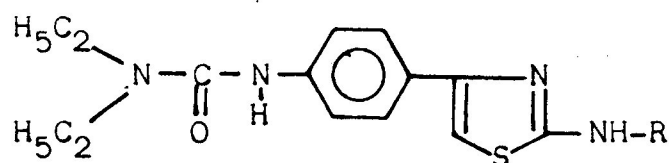


(VI)

Where,

$R, R' = \text{H, lower alkyl and } -\text{NO}_2$;
 $R^2 = \text{Lower alkyl, amino alkyl, etc.}$

On the basis of these observations regarding thiazoles and N,N-diethyl carbamoyl linkage from literature it was decided to incorporate the N,N-diethyl carbamoyl linkage into 2-(amino-substituted)-4-(p-amino-phenyl) thiazole (VII).



(VII)

R = Substituted-phenyl, heterocyclic, etc.

These compounds were prepared by condensing different thioureas with haloketone. In this series totally fourteen compounds have been prepared and subjected for antitubercular screening.

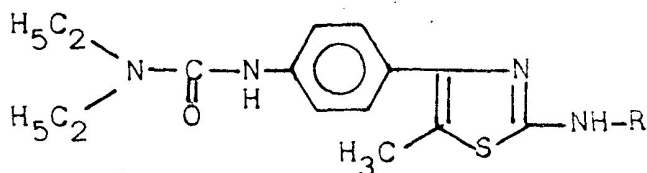
Section - C

2-(Substituted-anilino/heterocyclic amino)-4-(N,N-diethyl-N'-phenyl urea)-5-methyl thiazole :

Kulkarni et al.¹⁰ found that with introduction of the methyl group in the thiazole ring the antituberculosis activity increased and the 5-methyl derivatives were more active than the corresponding 2-methyl derivatives.

Hence, it was thought of interest to incorporate the methyl group at the fifth position of the 2-(substituted anilino/heterocyclic amino)-4-(substituted-phenyl)thiazole,

along with the N,N-diethyl carbamoyl linkage (VIII). Fourteen compounds were prepared in this series and subjected to anti-T.B. testing.



(VIII)

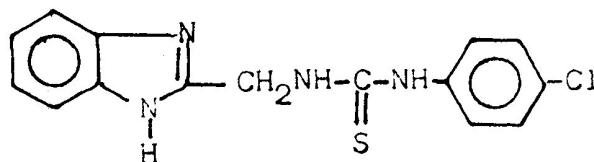
R = Substituted-phenyl, heterocyclic, etc.

Section - D

p-(Butyl)-p'-[4-(2,5-disubstituted) thiazolyl]-7-thiocarbanilide :

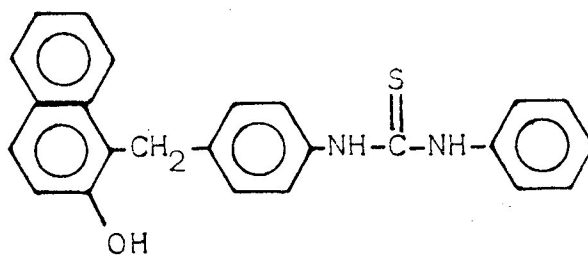
Thiourea derivatives have been found to exhibit wide therapeutic activities.¹¹

Benzimidazol-2-yl methyl thioureas (IX) are found to be active as antimicrobial agents.¹²



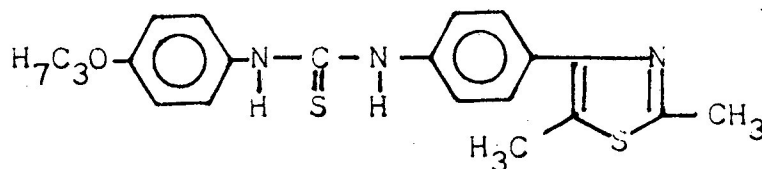
(IX)

Patel et al. reported hydroxynaphthyl benzyl aryl derivatives of thiourea (X) active against M. tuberculosis.¹³



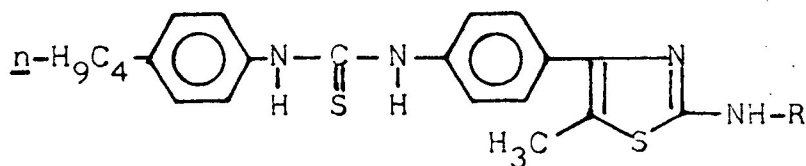
(X)

A substituted thiocarbanilide (XI) possessing a thiazole moiety was reported to show in vitro activity against M. tuberculosis.¹⁴



(XI)

Based on these data various p-butyl-p'-[4-(2,5-disubstituted thiazolyl)]-thiocarbanilides (XII) have been synthesized.



(XII)

where, R = Substituted-phenyl, heterocyclic, etc.

PART - IV

MICROBIAL TESTING :

Overall fifty new compounds have been synthesized. All compounds have been analysed for their elemental carbon, hydrogen and nitrogen percentage composition and are found to be correct.

These compounds were tested for their in vitro antitubercular activity against H₃₇Rv strain of Mycobacterium tuberculosis using Rake's method.¹⁵ Most of them inhibited the growth of M. tuberculosis at concentrations ranging from 100 µg/ml to 0.31 µg/ml. None of these compounds was found to be active to the level of standard drug Isoniazide which inhibits the growth of M. tuberculosis in vitro at concentration 0.04 µg/ml.

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